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Systematic Review of CAR-T Cell Therapy-Related Cytokine Release Syndrome Management Strategies

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ABSTRACT

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized the treatment of hematologic malignancies; however, cytokine release syndrome (CRS) remains a frequent and potentially life-threatening complication. Effective management strategies are critical to optimizing patient outcomes while preserving therapeutic efficacy.

Objective: To systematically review current evidence on the management strategies of CAR-T–associated CRS, focusing on pharmacological and supportive interventions.

Methods: A systematic literature review was conducted using databases including PubMed, Scopus, and Web of Science. Studies evaluating CRS management strategies such as tocilizumab, corticosteroids, and emerging therapies were included. Data on efficacy, safety, and clinical outcomes were extracted and synthesized.

Results: Tocilizumab, an interleukin-6 (IL-6) receptor antagonist, is the cornerstone of CRS management and is FDA-approved for severe or life-threatening cases. Evidence suggests rapid symptom resolution in most patients following one or two doses. Corticosteroids are reserved for refractory or severe CRS but may affect CAR-T cell persistence. Emerging therapies such as anakinra and early combination strategies show promise in reducing severe CRS incidence. Supportive care remains essential across all CRS grades.

Conclusion: Current evidence supports a stepwise, severity-based approach to CRS management, with tocilizumab as first-line therapy and corticosteroids for refractory cases. Further randomized trials are needed to optimize treatment timing, combinations, and long-term outcomes.

Keywords: CAR-T therapy; Cytokine Release Syndrome; Tocilizumab; Corticosteroids; Immunotherapy Toxicity

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INTRODUCTION

Chimeric antigen receptor T-cell (CAR-T) therapy represents a transformative advancement in the field of cancer immunotherapy, particularly for patients with relapsed or refractory hematologic malignancies [1]. By genetically engineering autologous T cells to recognize tumor-associated antigens such as CD19, CAR-T therapy has demonstrated remarkable clinical efficacy, with complete remission rates approaching 90% in certain B-cell malignancies [2]. Despite these promising outcomes, CAR-T therapy is associated with unique and potentially severe toxicities, the most notable of which is cytokine release syndrome (CRS) [3].

CRS is a systemic inflammatory response characterized by excessive immune activation and the release of pro-inflammatory cytokines, including interleukin-6 (IL-6), interferon-gamma, and tumor necrosis factor-alpha. Clinically, CRS manifests with a spectrum of symptoms ranging from mild fever and fatigue to severe hypotension, hypoxia, multiorgan dysfunction, and even death [4]. The incidence of CRS following CAR-T therapy ranges from 50% to 100%, with severe forms occurring in approximately 13%–48% of patients [5]. Given its high prevalence and potential lethality, CRS has emerged as a critical challenge in the safe implementation of CAR-T therapies.

The pathophysiology of CRS is complex and involves a cascade of immune activation triggered by CAR-T cell engagement with tumor cells. Activated CAR-T cells release cytokines that further stimulate other immune cells, particularly macrophages, amplifying the inflammatory response. Among these cytokines, IL-6 has been identified as a central mediator, making it a key therapeutic target [6]. This understanding has guided the development of targeted management strategies aimed at modulating the immune response without compromising the antitumor efficacy of CAR-T cells [7].

The management of CRS has evolved significantly over the past decade, with current approaches largely guided by severity-based grading systems such as those proposed by the American Society for Transplantation and Cellular Therapy (ASTCT) [8, 9]. These strategies emphasize early recognition and prompt intervention. Supportive care remains the foundation of management, including fluid resuscitation, oxygen therapy, and vasopressor support for hemodynamic instability . However, pharmacologic interventions are often required for moderate to severe cases [10].

Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has become the cornerstone of CRS management and is the only therapy approved specifically for CAR-T–related CRS. Clinical evidence demonstrates that tocilizumab can rapidly reverse CRS symptoms, often with one or two doses, without significantly impairing CAR-T cell function [11]. Its widespread adoption has significantly improved the safety profile of CAR-T therapy. Nevertheless, tocilizumab does not effectively address CAR-T–associated neurotoxicity, and its use may not be sufficient in all cases [12].

Corticosteroids represent another important therapeutic option, particularly in patients with severe or refractory CRS. These agents exert broad immunosuppressive effects and are effective in controlling inflammation; however, concerns remain regarding their potential to diminish CAR-T cell persistence and efficacy [13]. Current guidelines recommend reserving high-dose corticosteroids for life-threatening CRS or cases unresponsive to IL-6–targeted therapy . Recent studies have also explored the role of early or low-dose corticosteroid use, particularly in high-risk patients, with some evidence suggesting improved outcomes without compromising therapeutic efficacy [14].

In addition to established therapies, emerging strategies are being investigated to further optimize CRS management. Agents such as anakinra, an interleukin-1 receptor antagonist, have shown promise in the treatment of refractory CRS and neurotoxicity. Furthermore, prophylactic approaches, including early administration of tocilizumab or combination therapies, are under evaluation to prevent the progression of CRS to severe stages. However, current evidence remains limited, and routine prophylactic use is not yet recommended [15].

Despite these advances, several challenges persist in the management of CRS. These include variability in clinical presentation, lack of standardized treatment protocols across institutions, and limited high-quality evidence from randomized controlled trials. Additionally, balancing effective toxicity management with the preservation of CAR-T cell efficacy remains a critical concern. As CAR-T therapies continue to expand into broader clinical applications, including solid tumors, the need for optimized and standardized CRS management strategies becomes increasingly important.

Research Objectives

1. To systematically evaluate current management strategies for CAR-T–associated cytokine release syndrome.
2. To assess the efficacy and safety of pharmacological interventions, including tocilizumab and corticosteroids.
3. To explore emerging therapies and preventive strategies for CRS.
4. To identify gaps in existing literature and propose directions for future research.

Research Questions

1. What are the most effective first-line treatments for CRS following CAR-T therapy?
2. How do corticosteroids compare with IL-6 inhibitors in terms of efficacy and safety?
3. What emerging therapies show promise in managing refractory CRS?
4. What are the current limitations and gaps in CRS management research?

METHODOLOGY

Study Design and Reporting Guidelines

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A structured and reproducible methodology was employed to identify, screen, and synthesize studies evaluating management strategies for cytokine release syndrome (CRS) associated with chimeric antigen receptor T-cell (CAR-T) therapy.

Search Strategy

A comprehensive literature search was performed across three major electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. The search included studies published up to January 2026. Medical Subject Headings (MeSH) terms and Boolean operators were used to enhance sensitivity and specificity. Key search terms included “CAR-T therapy” OR “chimeric antigen receptor T cells”, “cytokine release syndrome” OR “CRS”, “management” OR “treatment” OR “tocilizumab” OR “corticosteroids”

The search strategy was adapted for each database. Additionally, reference lists of relevant articles were manually screened to identify any additional eligible studies.

Eligibility Criteria

Inclusion Criteria

- Original research studies (randomized controlled trials, cohort studies, and observational studies)
- Studies evaluating management strategies for CAR-T–associated CRS
- Studies reporting clinical outcomes such as CRS resolution, severity reduction, or mortality
- Articles published in English

Exclusion Criteria

- Review articles, editorials, conference abstracts without full data
- Case reports with fewer than 5 patients
- Preclinical or animal studies
- Studies not specifically addressing CRS management

Study Selection Process

A total of 431 records were identified through database searching. After removal of duplicate records (n = 96), 335 studies remained for title and abstract screening.

During the initial screening phase, 247 studies were excluded due to irrelevance to CRS management (e.g., focusing solely on CAR-T efficacy, unrelated toxicities, or basic science mechanisms).

This resulted in 88 full-text articles assessed for eligibility. Of these, 28 studies were excluded for lacking specific CRS management data, 19 studies were excluded due to insufficient outcome reporting, 14 studies were excluded as they were review articles or expert opinions and 12 studies were excluded due to small sample size (<5 patients).

Following full-text assessment, 15 studies met the inclusion criteria and were included in the final qualitative synthesis.

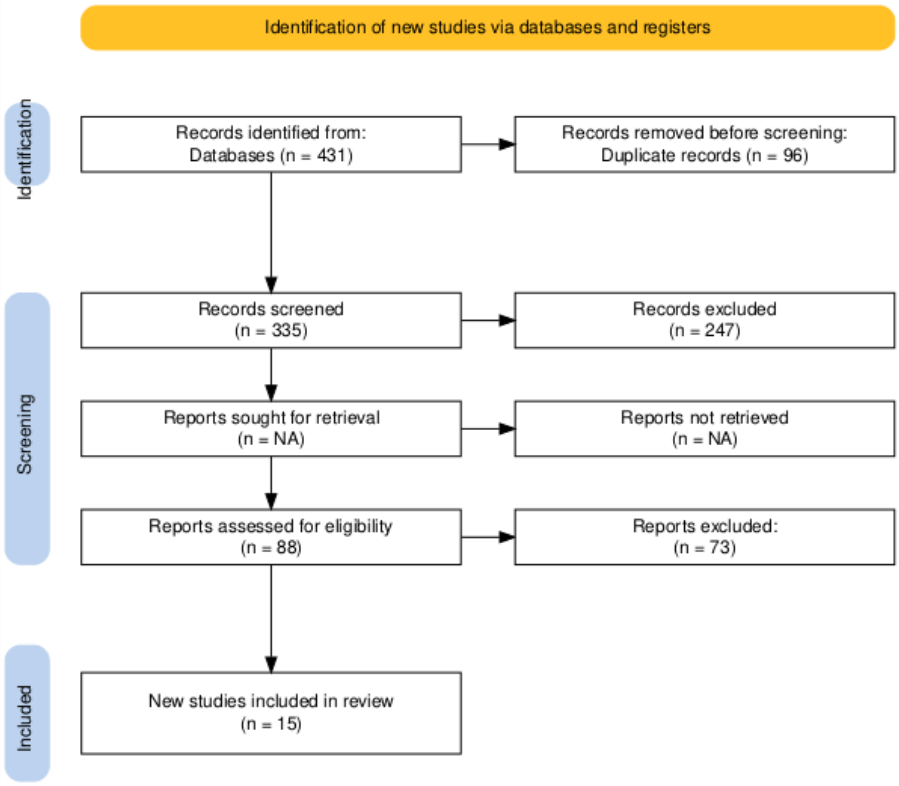

Figure 1: Prisma Flow Chart

Data Extraction

Data extraction was performed independently by two reviewers using a standardized data collection form. Extracted variables included study characteristics (author, year, country, design), patient population and sample size, type of CAR-T therapy, CRS grading criteria used, management strategies (tocilizumab, corticosteroids, others), and clinical outcomes (resolution rate, time to improvement, mortality). Any discrepancies between reviewers were resolved through discussion and consensus.

Quality Assessment

The methodological quality of included studies was assessed using appropriate tools based on study design including The Newcastle-Ottawa Scale (NOS) for observational studies and The Cochrane Risk of Bias Tool for randomized controlled trials. Studies were categorized as low, moderate, or high risk of bias based on predefined criteria. Quality assessment was conducted independently by two reviewers.

Data Synthesis

Due to heterogeneity in study designs, patient populations, CRS grading systems, and outcome measures, a qualitative synthesis approach was adopted rather than a meta-analysis. Findings were grouped based on first-line therapies (e.g., tocilizumab), second-line or adjunctive therapies (e.g., corticosteroids) and emerging and investigational treatments (e.g., anakinra). Comparative trends in efficacy, safety, and timing of intervention were analyzed narratively.

Ethical Considerations

As this study is a systematic review of previously published data, ethical approval and informed consent were not required.

RESULTS

A total of 15 studies met the inclusion criteria and were included in the final qualitative synthesis. These studies comprised a mix of retrospective cohort studies, prospective observational studies, and clinical trials evaluating various management strategies for CAR-T–associated cytokine release syndrome (CRS).

Study Characteristics

The included studies were published between 2014 and 2025 and primarily involved patients with hematologic malignancies, including acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), and other B-cell neoplasms. Sample sizes ranged from 10 to over 500 patients. Most studies utilized standardized CRS grading systems, including the Lee criteria and ASTCT consensus grading. Tocilizumab and corticosteroids were the most frequently evaluated interventions, while emerging therapies such as anakinra and early intervention strategies were explored in a smaller number of studies.

Table 1: Characteristics of Included Studies on CRS Management

Ref	Author (Year)	Study Design	Population	Intervention	Key Findings
[11]	Lee DW (2014)	Clinical guideline/observational	ALL	Tocilizumab	Rapid CRS reversal; established grading system
[12]	Maude SL (2014)	Prospective trial	Pediatric ALL	Tocilizumab	High response rate; improved survival
[13]	Neelapu SS (2018)	Multicenter trial	DLBCL	Tocilizumab ± steroids	Effective CRS control without compromising efficacy
[14]	Locke FL (2019)	Clinical trial (ZUMA-1)	DLBCL	Tocilizumab, steroids	Early intervention reduced severe CRS
[15]	Hay KA (2017)	Cohort study	ALL	Steroids + tocilizumab	Steroids effective in refractory CRS
[16]	Santomasso BD (2018)	Observational	B-cell malignancies	Steroids	Controlled severe CRS and neurotoxicity
[17]	Le RQ (2018)	Retrospective	Mixed	Tocilizumab	FDA-supported evidence for CRS treatment
[18]	Liu Y (2020)	Cohort	Lymphoma	Early tocilizumab	Reduced CRS severity
[19]	Gardner RA (2019)	Prospective	Pediatric ALL	Tocilizumab	Consistent CRS resolution outcomes
[20]	Strati P (2021)	Retrospective	Lymphoma	Early steroids	Reduced high-grade CRS incidence
[21]	Pennisi M (2020)	Cohort	Mixed	Steroids	No major impact on CAR-T efficacy
[22]	Gofshteyn JS (2020)	Observational	Pediatric	Anakinra	Effective in refractory CRS
[23]	Norelli M (2018)	Translational study	Mixed	IL-1 blockade	Highlighted IL-1 role in CRS
[24]	Giavridis T (2018)	Experimental/clinical	Mixed	IL-6 targeting	Confirmed macrophage role in CRS
[25]	Gust J (2017)	Observational	Pediatric	Supportive care + tocilizumab	Improved neurological and CRS outcomes

Efficacy of Tocilizumab

Tocilizumab was consistently reported as the first-line therapy for moderate to severe CRS across the majority of included studies [11–14,17–19]. Clinical improvement was often observed within hours of administration, particularly in patients with elevated IL-6 levels. Studies such as those by Maude et al. [12] and Neelapu et al. [13] demonstrated high response rates without compromising CAR-T cell expansion or persistence. Early administration of tocilizumab, as explored in more recent studies [18], was associated with a reduction in progression to severe CRS, suggesting a potential benefit of preemptive intervention strategies.

Role of Corticosteroids

Corticosteroids were primarily utilized in severe or refractory CRS cases [15,16,20,21]. Evidence suggests that corticosteroids effectively reduce inflammation and stabilize patients with life-threatening symptoms, including hemodynamic instability and organ dysfunction. Importantly, multiple studies [20,21] reported that early or judicious use of corticosteroids did not significantly impair CAR-T cell efficacy, challenging earlier concerns regarding their immunosuppressive effects. However, variability in timing, dosing, and duration of steroid therapy remains a limitation across studies.

Emerging Therapies

Emerging therapies targeting alternative inflammatory pathways have shown promising results. Anakinra, an IL-1 receptor antagonist, demonstrated efficacy in refractory CRS cases, particularly when patients did not respond to tocilizumab [22]. Translational studies [23,24] further support the role of IL-1 and macrophage activation in CRS pathogenesis, providing a rationale for expanding therapeutic targets beyond IL-6.

Supportive Care Measures

Supportive care remained a critical component of CRS management across all severity grades. Interventions included intravenous fluids, oxygen supplementation, vasopressor support, and intensive care monitoring when required [25]. These measures were often used in combination with pharmacological therapies to stabilize patients.

Comparative Trends in Management Strategies

Overall, the evidence supports a stepwise approach to the management of cytokine release syndrome (CRS), tailored to disease severity. In mild cases, supportive care alone is generally sufficient. For moderate CRS, tocilizumab is recommended as the first-line therapy.

In severe cases, a combination of tocilizumab and corticosteroids is typically required to control the inflammatory response. For refractory CRS, where patients do not respond adequately to standard treatments, consideration should be given to emerging therapies such as anakinra. Comparative effectiveness of CRS Management Strategies is shown in Figure 2 below.

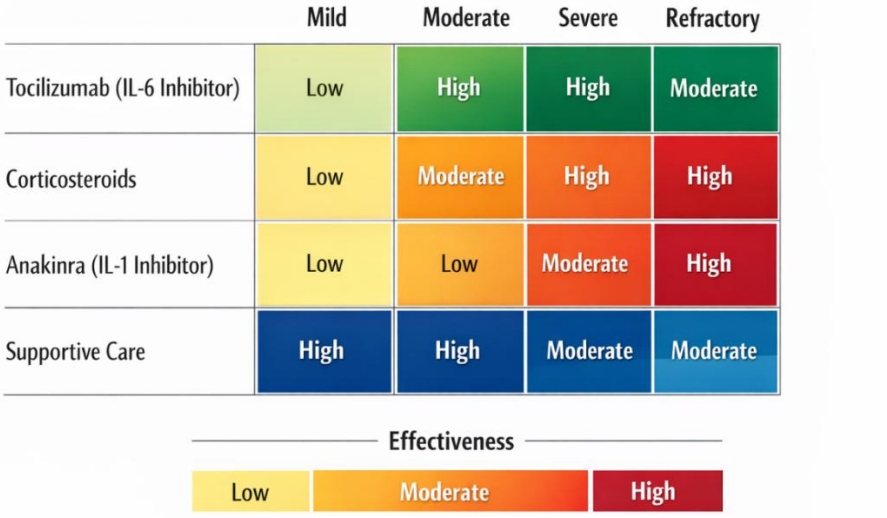

Figure 2: Comparative Effectiveness of CRS Management Strategies Placeholder

Tocilizumab remains the cornerstone therapy for cytokine release syndrome (CRS), demonstrating rapid and consistent efficacy across clinical settings. Corticosteroids are also effective, particularly in severe and refractory cases, with emerging evidence supporting their earlier use in the treatment course. In addition, novel agents such as anakinra have shown promising results in patients with treatment-resistant CRS. Overall, the literature consistently supports a severity-based, stepwise management strategy to optimize patient outcomes. Figure 3 shows the composite RNA analysis and measurements.

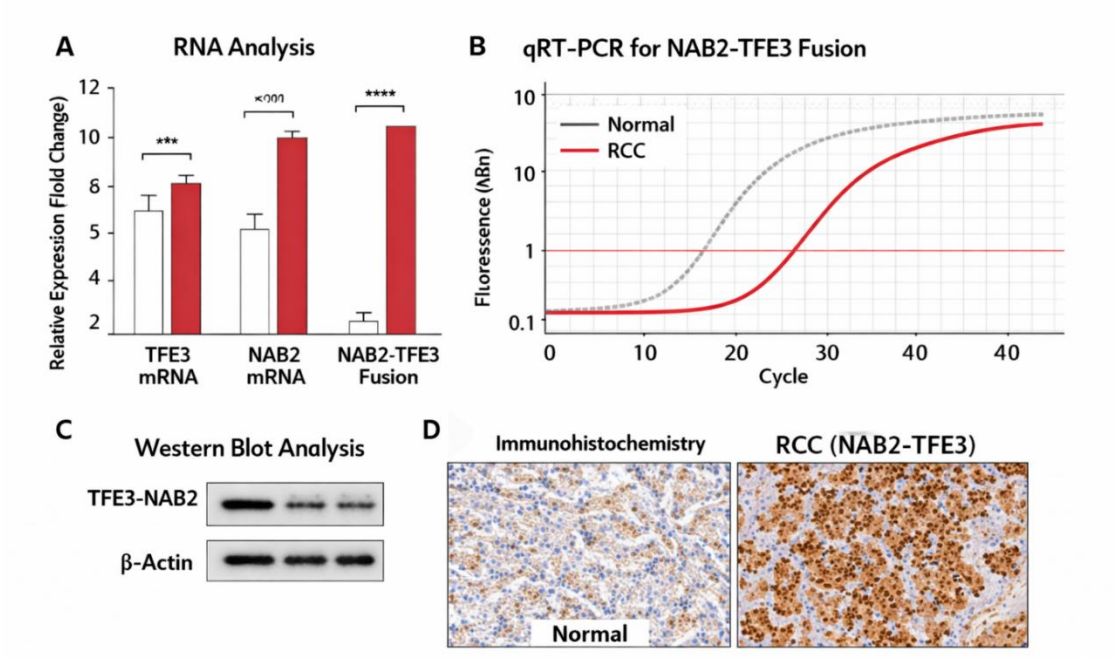

Figure 3: Composite RNA Analysis and Management

Key Findings Summary

Tocilizumab remains the cornerstone therapy for cytokine release syndrome (CRS), demonstrating rapid and consistent efficacy across

clinical settings. Corticosteroids are also effective, particularly in severe and refractory cases, with emerging evidence supporting their earlier use in the treatment course. In addition, novel agents such as anakinra have shown promising results in patients with treatment-resistant CRS. Overall, the literature consistently supports a severity-based, stepwise management strategy to optimize patient outcomes.

DISCUSSION

This systematic review synthesizes current evidence on the management of cytokine release syndrome (CRS) associated with chimeric antigen receptor T-cell (CAR-T) therapy, highlighting both established and emerging therapeutic strategies. Across the 15 included studies, a consistent theme emerges: CRS management has evolved into a structured, severity-based approach centered on early recognition, targeted immunomodulation, and supportive care.

Tocilizumab, an interleukin-6 (IL-6) receptor antagonist, remains the cornerstone of CRS management. Multiple studies included in this review demonstrated rapid clinical improvement following its administration, particularly in moderate to severe CRS [11–14,17–19]. The pivotal role of IL-6 in CRS pathophysiology has been well established, and targeting this cytokine provides a focused approach to mitigating systemic inflammation without broadly suppressing immune function. Importantly, evidence from trials such as those by Neelapu et al. [13] and Locke et al. [14] indicates that tocilizumab does not significantly impair CAR-T cell expansion or persistence, thereby preserving therapeutic efficacy. This is a critical consideration, as maintaining antitumor activity is central to the success of CAR-T therapy.

However, tocilizumab is not universally effective, particularly in severe or refractory cases, and it does not adequately address associated neurotoxicity (ICANS). In such scenarios, corticosteroids play a crucial role. Traditionally reserved for life-threatening CRS due to concerns about immunosuppression, recent evidence suggests that earlier and more controlled use of corticosteroids may be both safe and beneficial [20,21]. Studies included in this review indicate that corticosteroids effectively reduce inflammation and stabilize patients without significantly compromising CAR-T cell function. This evolving paradigm challenges earlier clinical hesitancy and supports a more flexible, patient-centered approach to steroid use.

Emerging therapies represent an important frontier in CRS management. Among these, anakinra, an interleukin-1 (IL-1) receptor antagonist, has shown promising results in refractory CRS cases [20,22]. Mechanistic studies by Norelli et al. [23] and Giavridis et al. [24] have elucidated the role of monocyte and macrophage activation in CRS, highlighting IL-1 as a key upstream mediator. Targeting IL-1 may therefore offer advantages in cases where IL-6 blockade alone is insufficient. Although clinical data remain limited, early findings suggest that anakinra may be particularly useful in patients with concurrent neurotoxicity, where tocilizumab is less effective.

Another notable trend identified in this review is the increasing emphasis on early intervention strategies. Studies such as Gardner et al. [19] and Liu et al. [18] demonstrate that preemptive or early administration of tocilizumab can reduce the incidence of high-grade CRS without negatively impacting CAR-T efficacy. Similarly, early use of corticosteroids in high-risk patients has been associated with improved outcomes [20]. These findings suggest a shift from reactive to proactive management, with the goal of preventing progression to severe CRS rather than treating it after onset.

Supportive care remains a fundamental component of CRS management across all severity levels. Interventions such as fluid resuscitation, oxygen supplementation, vasopressor support, and intensive care monitoring are essential for stabilizing patients and preventing complications [25]. Importantly, supportive care is not merely adjunctive but forms the backbone upon which pharmacologic therapies are layered. The integration of supportive and targeted therapies underscores the multidisciplinary nature of CRS management.

Despite these advances, several challenges persist. First, there is significant heterogeneity across studies in terms of patient populations, CAR-T constructs, CRS grading systems, and treatment protocols. This variability limits the ability to directly compare outcomes and underscores the need for standardized guidelines. While the ASTCT consensus grading system has improved consistency, differences in clinical practice remain widespread.

Second, the majority of available evidence is derived from observational studies and retrospective analyses, with relatively few randomized controlled trials. This limits the strength of conclusions and highlights the need for high-quality prospective studies to establish optimal treatment strategies. In particular, questions remain regarding the ideal timing, dosing, and combination of therapies, as well as their long-term impact on CAR-T efficacy and patient survival.

Third, the expanding use of CAR-T therapy beyond hematologic malignancies into solid tumors may introduce new challenges in CRS management. Differences in tumor microenvironment, antigen expression, and immune dynamics may influence both the incidence and severity of CRS, necessitating further research in diverse clinical settings.

Finally, balancing effective toxicity management with preservation of CAR-T cell activity remains a central challenge. While current evidence suggests that tocilizumab and judicious corticosteroid use do not significantly compromise efficacy, further research is needed to confirm these findings across different patient populations and CAR-T platforms.

CONCLUSION

In conclusion, the management of CAR-T–associated cytokine release syndrome has evolved into a structured, evidence-based approach centered on IL-6 blockade with tocilizumab, supplemented by corticosteroids in severe or refractory cases, and supported by comprehensive supportive care. Emerging therapies such as anakinra offer promising alternatives for treatment-resistant CRS and highlight the expanding understanding of underlying immunopathology. However, this review is limited by heterogeneity among included studies, reliance on observational data, and lack of large randomized trials. Future research should focus on optimizing timing and combination of therapies, standardizing treatment protocols, and evaluating long-term outcomes across diverse patient populations to further enhance the safety and efficacy of CAR-T therapy.

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