Infectious complications, immune reconstitution, and infection prophylaxis after CD19 chimeric antigen receptor T-cell therapy

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INTRODUCTION

CD19-targeted chimeric antigen receptor (CAR) T-cell becomes a breakthrough therapy providing excellent remission rates and durable disease control for patients with relapsed/refractory (R/R) hematologic malignancies. However, CAR T-cells have several potential side effects including cytokine release syndrome, neurotoxicities, cytopenia, and hypogammaglobulinemia. Infection has been increasingly recognized as a complication of CAR T-cell therapy. Several factors predispose CAR T-cell recipients to infection. Fortunately, although studies show a high incidence of infection post-CAR T-cells, most infections are manageable. In contrast to patients who undergo hematopoietic stem cell transplant, less is known about post-CAR T-cell immune reconstitution. Therefore, evidence regarding antimicrobial prophylaxis and vaccination strategies in these patients is more limited. As CAR T-cell therapy becomes the standard treatment for R/R B lymphoid malignancies, we should expect a larger impact of infections in these patients and the need for increased clinical attention. Studies exploring infection and immune reconstitution after CAR T-cell therapy are clinically relevant and will provide us with a better understanding of the dynamics of immune function after CAR T-cell therapy including insights into appropriate strategies for prophylaxis and treatment of infections in these patients. In this review, we describe infections in recipients of CAR T-cells, and discuss risk factors and potential mitigation strategies.

Incidence and characteristics of infection after CAR T-cell therapy

Data on infections following CAR T-cell therapy have been mostly derived from single-center retrospective studies [13–19] in patients treated with CD19 CAR T-cells as well as some information from prospective clinical trials. With the recent approval of BCMA CAR T-cells, there is also emerging data in infectious complications in patients treated with these products. Patients with hematologic malignancies who undergo CAR T-cell therapy can develop infections at several timepoints after treatment. CAR T-cell therapy may be divided into three phases including the initiation of lymphodepletion (LD) chemotherapy, early post-CAR T-cells (day 0 to +30), and late phase after CAR T-cells (day +30 to +365 or beyond) (Fig. 1) [20]. The pattern of infections and dominant causative pathogens during each period varies based on the primary component of immune deficiency state at various time points.

Infections in patients who undergo CD19 CAR T-cell therapy

The incidence of infections in patients receiving CD19 CAR T-cells varies from 18 to 56% in the prospective registration clinical trials and 20–60% in retrospective cohort analyses [2–8, 13–17, 21–30].

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However, differences in incidence among studies could be attributed to several factors, including patient-related factors, CAR T-cell-related factors, and the definition and duration of follow up in each study. Table 1 summarizes the incidence and characteristics of infections after CD19 CAR T-cells from phase II/III prospective clinical trials.

In addition, several retrospective cohort studies have reported real-world data on infectious complications and outcomes in patients treated with CAR T-cells (Table 2). In a retrospective report by Hill et al. describing a single-center experience of infectious complications in patients with various B lymphoid malignancies treated with CD19 CAR T-cells, 23% of patients developed infection within the first 28 days after CAR T-cell infusion, which translated into an infection density of 1.19 infections for every 100 days at risk [13]. Patients with B-ALL had a higher infection density compared to other hematologic malignancies. Park et al. reported a 40% incidence of infections during the early phase (day 0–30) in adult B-ALL patients who received CD19–28z CAR T-cell therapy [16]. There were 20 bacterial and 16 viral infections [16]. The incidence of infections in pediatric, adolescent, and young adult patients with B-ALL who received CD19 CAR T-cells was similar to adult patients. According to Vora et al., 54% of patients developed infectious complications within the first 90 days, with most occurring within the first 28 days [18].

In patients with lymphoma, Wudhikarn et al. reported real-world data on infectious complications in 60 consecutive patients with diffuse large B cell lymphoma (DLBCL) treated with axicabtagene ciloleucel or tisagenlecleucel [17]. The 1-year cumulative incidence of infection was 63.3% with bacterial infections being the most common (1-year incidence 57.2%). Other reports also demonstrated similar patterns and incidence of infections in patients with DLBCL treated with CD19 CAR T-cells [18, 28, 31].

Data on infectious complications in patients with MM treated with CAR T-cells are still limited. Unlike CD19 CAR T-cells, viral infection is the most common infectious complication followed by bacterial and fungal infections. In a recent report of 55 patients with R/R MM patients treated with BCMA CAR T-cells, 53% developed infection within the first 6 months (53% viral, 40% bacterial, and 6% fungal) [32]. Approximately half of the infectious events occurred within the first 100 days. Josyula et al. also reported the effect of BCMA CAR T-cells on humoral immunity and risk of infection in patients with R/R multiple MM [33]. The incidence of early infections (<30 days post-CAR T-cell therapy) appeared to be less common than for B lymphoid malignancy treated with CD19 CAR T-cells, whereas late infections were more frequent. In addition, viral infections were more frequent than bacterial infections.

**Bacterial infections**
Most retrospective data describe a similar pattern of infections after CAR T-cells. During the early post-CAR T-cell period (including LD chemotherapy and the first 30 days after infusion), the most common pathogens are bacteria with neutropenia being a notable risk factor. Bacterial infections account for up to 40–50% of infections and typically occur within the first 2 weeks during the neutropenia period, presenting either as bacteremia or organ-specific infection. Bloodstream infection including central venous catheter-associated infection, gastrointestinal, and respiratory tracts are the three most common sites of infection. Common bacterial infections (especially the first 30 days) include Clostridium infection, gram-negative Enterobacteriaceae, and gram-positive enterococci [15, 17]. These patients are at risk of developing multi-drug resistant nosocomial bacterial infection due to previous history of heavy exposure to broad-spectrum antibiotics, which may predispose them to microbiome alteration and colonization of drug-resistant pathogens. In one study, 4 of 24 bacterial infections during the first 28 days post-CAR T-cell infusion were due to fluoroquinolone-resistant gram-negative bacteria [13].

**Viral infections**
In contrast to bacterial pathogens, viruses are more common later in the course after CD19 CAR T-cell therapy. After day +30, lymphopenia (either B or T lymphocytes) and hypogammaglobulinemia become two critical components of immune dysfunction. Respiratory viral pathogens are the most common pathogens especially in the later phase of CAR T-cell therapy with most events being mild or moderate in severity with some patients developing severe infection. In addition to B cell aplasia, a significant proportion of patients has profound CD4 lymphopenia, and delayed reactivation of herpes viruses is frequently observed over 6–12 months after CD19 CAR T-cell infusion. Cytomegalovirus (CMV) reactivation (including Herpes virus) was reported in ~1–2% but the real incidence is not known since routine monitoring of CMV varies among centers. Most reported cases presented as CMV viremia whereas CMV disease was uncommon but has been increasingly reported with some fatal cases being described [31, 34, 35].
| CD19-positive B cell Non-Hodgkin lymphoma | Acute B-cell Lymphoblastic Leukemia |
|------------------------------------------|-----------------------------------|
| **ZUMA-1 (2)** | **ELARA (24)** |
| CD19-positive B cell Non-Hodgkin lymphoma | **ZUMA-2 (5)** |
| ZUMA-7 (23) | **ZUMA-5 (7)** |
| TRANSFORM (24) | **ELIANA (22)** |
| ZUMA-12 (25) | **ZUMA-3 (6)** |

| Patient Population | Number of patients | Median duration of follow-up | Overall infection | Bacterial infection | Viral infection | Fungal infection |
|--------------------|--------------------|-----------------------------|------------------|-------------------|---------------|----------------|
| R/R DLBCL, R/R PMBC, R/R tFL | 105 | 12.3 months | Any Grades | Any Grades | Any Grades | Any Grades |
| R/R DLBCL, R/R HGBL, R/R tFL | 111 | 24.9 months | NR | Any Grades | Any Grades | Any Grades |
| R/R DLBCL, R/R HGBL, R/R FL Gr 3, R/R HGBL, R/R PMBC | 269 | 6 months | NR | Any Grades | Any Grades | Any Grades |
| R/R DLBCL, R/R HGBL, R/R tFL | 92 | 15 months | NR | Any Grades | Any Grades | Any Grades |
| R/R DLBCL, R/R HGBL, R/R FL | 40 | 16.6 months | NR | Any Grades | Any Grades | Any Grades |
| R/R MCL | 68 | 13.1 months | NR | Any Grades | Any Grades | Any Grades |
| R/R FL | 148 | 16.4 months | NR | Any Grades | Any Grades | Any Grades |
| R/R FL (Age < 25 years) | 97 | 17.5 months | NR | Any Grades | Any Grades | Any Grades |
| R/R B-ALL | 75 | 17.5 months | NR | Any Grades | Any Grades | Any Grades |

**Note:** R/R relapse/refractory, DLBCL diffuse large B cell lymphoma, PMBC primary mediastinal B cell lymphoma, tFL transformed follicular lymphoma, HGBL high grade B cell lymphoma, NHL non-Hodgkin lymphoma, MCL mantle cell lymphoma, ALL acute lymphoblastic leukemia, NR not reported, CMV cytomegalovirus, HZV Herpes Zoster virus, pt patient.
### Table 2. Data of infectious complications in patients with B lymphoid malignancy treated with CD19 CAR T-cell from retrospective studies.

| Diagnosis | Number of patients | Age group | Median prior lines of treatment | Lymphodepletion | Baseline parameters | CAR T product | Observation duration | All infection | Bacterial infection | Viral infection | Fungal Infection | Receipt of GCSF | Antibacterial prophylaxis | Antiherpetic prophylaxis |
|-----------|--------------------|-----------|---------------------------------|-----------------|---------------------|------------------|-----------------------|--------------|--------------------|----------------|-----------------|----------------|-----------------------------|------------------------|
| NHL       | 133                | Adult     | 4 (1-11) 1-11                   | Varied          | NR                  | CD19-28z CAR T    | 90 days post-CAR-T   | 101 events 40 pt | 45 events 27 pt |                |                 |                |                           |                        |
| ALL       | 53                 | Adult     | 3 (IQR 2-7) 2-11               | Cyclophosphamide, Fludarabine/Cyclophosphamide | 16 (28%) NR | CD19-28z CAR T    | 180 days post-CAR-T   | 365 days post-CAR-T | 90 days post-CAR-T | 2 years post-CAR-T | Minimum 1 year follow up post-CAR-T | 180 days post-CAR-T | 60 days post-CAR-T |
| CLL       | 85                 | Adult     | 3 (1-11) 1-11                  | Fludarabine/Cyclophosphamide | 23 (27%) 1-11 | CD19-28z CAR T    | 2 years post-CAR-T   | 2 events 12 pt     | 9 events 11 pt     |                |                 |                |                           |                        |
|          |                    | Pediatric | 83 (100%) 1-11                 | Varied          | 46 (55%) 1-11      | Varied (According to product but mostly Fludarabine/ cyclophosphamide) | Minimum 1 year (median 28 months) | 26 events 18 pt | 18 events 15 pt |                |                 |                |                           |                        |
|          |                    | Adult     | 31 (100%) 1-11                 | Fludarabine/Cyclophosphamide | 11 (36%) 1-11 | Varied (According to product but mostly Fludarabine/ cyclophosphamide) | Minimum 1 year follow up post-CAR-T | 12 events 12 pt | 12 events 18 pt |                |                 |                |                           |                        |
|          |                    | Adult     | 86 (100%) 1-11                 | Fludarabine/Cyclophosphamide | 39 (45%) 1-11 | Varied (According to product but mostly Fludarabine/ cyclophosphamide) | Minimum 1 year follow up post-CAR-T | 24 events 12 pt | 24 events 18 pt |                |                 |                |                           |                        |
|          |                    | Adult     | 60 (100%) 1-11                 | Fludarabine/Cyclophosphamide | 17 (28%) 1-11 | Varied (According to product but mostly Fludarabine/ cyclophosphamide) | Minimum 1 year follow up post-CAR-T | 24 events 12 pt | 24 events 18 pt |                |                 |                |                           |                        |
|          |                    | Adult     | 41 (100%) 1-11                 | Fludarabine/Cyclophosphamide | 21 (51%) 1-11 | Varied (According to product but mostly Fludarabine/ cyclophosphamide) | Minimum 1 year follow up post-CAR-T | 24 events 12 pt | 24 events 18 pt |                |                 |                |                           |                        |
|          |                    | Adult     | 60 (100%) 1-11                 | Fludarabine/Cyclophosphamide | 31 (35%) 1-11 | Varied (According to product but mostly Fludarabine/ cyclophosphamide) | Minimum 1 year follow up post-CAR-T | 24 events 12 pt | 24 events 18 pt |                |                 |                |                           |                        |
|          |                    | Pediatric and adult | 88 (100%) 1-11 | Fludarabine/Cyclophosphamide | 31 (35%) 1-11 | Varied (According to product but mostly Fludarabine/ cyclophosphamide) | Minimum 1 year follow up post-CAR-T | 24 events 12 pt | 24 events 18 pt |                |                 |                |                           |                        |

**Legend:**
- NR: Not reported
- IQR: Interquartile range
- GCSF: Granulocyte colony-stimulating factor
- IVIG: Immunoglobulin
- CAR T: Chimeric antigen receptor T-cell

**References:**
- Hill et al. [13]
- Park et al. [16]
- Logue et al. [18]
- Vora et al. [30]
- Cordeiro et al. [28]
- Wudhikarn et al. [17]
- Baird et al. [14]
- Korell et al. [31]
- Dayagi et al. [29]
Recently, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 or COVID-19) has emerged as one of the major infectious disease threats. Patients with hematologic malignancies including patients who undergo cellular therapy (either stem cell transplant or CAR T-cell therapy) are among the highest risk group of developing severe SARS-CoV-2 infection and having prolonged viral clearance time [36–38]. Viral shedding time of SARS-CoV-2 virus in patients undergoing transplantation and CAR-T cells could be up to 2 months [39]. Data from the European Hematology Association (EHA) reported an incidence of COVID-19 of 4.8% with the median time from CAR T-cell therapy to infection of 169 days [40]. Severe infection was observed in 67% and the COVID-19-related mortality was around 50% highlighting that overall outcome of COVID-19 infection after CAR T-cell therapy was poor [41]. Lymphopenia was an independent factor correlating with degree of COVID-19 severity.

**Fungal infections**

Fungal infection has been reported sporadically [42]. The most important risk factor for fungal infections is the duration of neutropenia (and in some cases lymphopenia) and prolonged course of systematic corticosteroid for severe CAR T-cell associated adverse reactions. Fungal infections are uncommon with an incidence between 1 and 5% [13, 17, 28, 42, 43]. Fatal cases from severe yeast and invasive mold infection have been increasingly reported [42, 43]. Pneumocystis infection is rarely observed, and this could represent routine use of effective prophylaxis.

In summary, most studies show similar incidences and patterns of infections after CAR T-cell therapy. Infections, especially severe infections and bacterial infections are more common during the first 30 days. After day +30, bacterial infections remain common but become less frequent and less severe. In the later phase, viruses are seen more often and are usually mild to moderate in severity. Other infections, i.e., fungal or pneumocystis infections are less frequently observed likely due to effective prophylactic strategies but can still be seen in patients with prolonged neutropenia or exposure to intensive and extended immunosuppressive treatments for CAR T-cell-associated complications.

**RISK FACTORS OF INFECTIOUS COMPLICATIONS IN PATIENTS RECEIVING CAR T-CELL THERAPY**

Hill and Seo recently provided an overview of patients with high risk of infectious complications after CAR T-cell therapy [20]. The underlying predisposing factors for infection can be divided into host-related and CAR T-cell-related factors.

1. **Host-related factors:** Patients who undergo CAR T-cell therapy typically have relapsed/refractory disease and have received several lines of therapy. The extent of prior therapy along with the impact on the immune system of the primary malignancy can lead to varying degrees of immune exhaustion, decreased bone marrow reserve with preexisting cytopenia, and delays in post-treatment immune recovery. Several studies demonstrated that a significant proportion of patients had baseline leukopenia and hypogammaglobulinemia even before CAR T-cell therapy. The underlying primary hematologic malignancy may also play a role in the risk of infection. For example, among B cell lymphoid neoplasms treated with CD19 CAR T-cells, there was evidence showing that patients with B-ALL tended to carry a higher risk of infection post-CAR T-cell therapy than CLL and B-NHL [13]. In addition, history of previous infection prior to CAR T-cell therapy has been shown in many studies to be strongly associated with increased risk of infection after CAR T-cells [17, 18, 44]. Age may also impact the patterns and incidence of infections [29]. In adult B-ALL, Park et al. reported an infection incidence of 42% during the first...
30 days with bacteria being the most common pathogen (30%) [16]. In contrast, in another retrospective study in pediatric and young adult B-ALL treated with CD19 CAR T-cells, viral infections were as common as bacterial infections during the first 28 days [18]. Receipt of bridging therapy, impaired performance status, history of prior HCT, underly-
ing medical co-morbidities, and preexisting hypogamma-
globulinemia were shown to be risk factors for infections
after CAR T-cells in some studies [18, 45, 46].

2. CAR T-associated factors: As noted above, a proportion of
patients develop profound and prolonged neutropenia after
CAR T-cell therapy, which will place them at increased risk of
bacterial infection. Aside from LD chemotherapy, CRS and
ICANS represent two well-established CAR T-cell-associated
complications that can lead to immune dysregulation.
Several studies have shown that both severe CRS and
ICANS are associated with infections, severe infections, and
bloodstream infections both in ALL and B-NHL patients
[13, 15, 16]. Severe CRS and ICANS are risk factors for
prolonged or recurrent cytopenia, which in turn results in
increased risk of infections [47–49].

Moreover, as the management of severe CRS generally involves
cytokine-directed therapy such as tocilizumab and systemic
corticosteroid, this may impact the ability of the host immune
system to mount appropriate response to pathogens. Initial data
from a small single-center retrospective study and data from
rheumatoid arthritis suggested an association between tocilizumab
and increased risk of infection [15, 50]. However, recent findings
from a CIBMTR study did not support an association between
tocilizumab use and infection in patients who were treated with
CD19 CAR T-cell therapy [51]. The impact of systemic corticosteroid,
either cumulative dose or duration, on the risk of infectious
complication and outcomes after CAR T-cells has been heavily
investigated. Several studies showed that steroid exposure is a major
risk factor for infectious complications and inferior survival after CAR
T-cell therapy [15, 17, 52, 53]. However, there are conflicting results
on the effects of tocilizumab and corticosteroid on infection risk,
which may be attributable to the definition of infections,
antimicrobial prophylaxis, underlying diagnosis, and selection bias
among studies. Duration of neutropenia and lymphopenia are other
potential predisposing factor for fungal infection [54]. Whether other
cytokine-directed therapy for CRS, i.e., anti-IL1 inhibitor would
increase the risk of infection is not yet known.

Other factors associated with infections include CAR T-cell dose
and target of CAR T-cell product. Higher CAR T-cell dose has been
associated with a higher risk of infections in some studies [13].
B-cell aplasia, plasma cell depletion, and resultant hypogamma-
globulinemia are inevitable side effects of CD19/BCMA CAR T-cells
and could predispose patients to infectious complications [55, 56].
Walti et al. demonstrated that BCMA-targeted CAR T-cells may
develop more profound hypogammaglobulinemia and low level
of pathogen-specific immunoglobulin including poorer response
to immunization compared to CD19 CAR T-cell products [57, 58].
In conclusion, both patients and CAR T-associated factors lead to a
cumulative immunosuppressive state, which predisposes CAR
T-cell recipients to infections.

HEMATOLOGIC AND IMMUNE RECOVERY AFTER CAR T-CELL
THERAPY

Although our knowledge of immune reconstitution in hematopoietic stem cell transplant (HSCT) has been well established,
similar data after CAR T-cell therapy is still very limited. Most
available data have been derived from patients treated with CD19
CAR T-cells. Besides B cell and plasma cell depletion secondary to
on-target off-tumor effects, cytopenia of other cell lineages is a
well-documented CAR T-cell-related adverse event. Several studies
have demonstrated high incidence of cytopenia after CAR T-cells
[14, 42, 47, 59–62]. The mechanism of cytopenia is multifactorial
and not yet well understood [63, 64]. Rejeski et al. characterize the
pattern of hematologic recovery in patients with R/R DLBCL after
axicabtagene ciloleucel into three different categories: quick
recovery, intermittent recovery, and aplastic. In this study, the
authors reported profound neutropenia (ANC < 100) in 72% of
patients and prolonged (21 days or longer) neutropenia in 64% of
patients [48]. Intermittent hematologic recovery was the dominant
phenotype of patients in this cohort. In another study, Fried et al.
also demonstrated the commonly observed biphasic nature of
hematologic toxicities in patients with B cell lymphoid malignancy
-treated with CD19 CAR T-cells [60]. Results from clinical trials
showed an incidence of delayed neutropenia after day +28 post-
CAR T-cell ranging between 20 and 80% [2–4, 65]. In a
retrospective single-center study from the Memorial Sloan
Kettering, Jain et al. highlighted the characteristics and risk factors
of cytopenia including patterns of hematologic recovery after various
types of CAR T-cells in different hematologic malignancy
diagnoses [47]. In this study, ~30% recovered white blood count
(WBC) and neutrophil count at 1-month post-CAR T infusion. In
addition, only 13% and 30% of patients had WBC and neutrophil
normalization, respectively, at 1 year after CAR T-cell therapy. Risk
factors for delayed hematologic recovery beyond 30 days after
infusion were severe CRS and ICANS. Other predisposing factors
for prolonged/delayed cytopenia include baseline pre-CAR T
cytopenia, early-onset CRS, higher grade CRS, a recent history of
HSCT prior to CAR T-cell therapy, higher ferritin/CRP level, and
decreased SDF-1 level [47, 60, 66, 67].

In addition to neutropenia, lymphopenia especially B cell aplasia are
hallmarks of CD19-targeted CAR T-cells. The duration of B
lymphopenia may be a surrogate of CAR T-cell persistence and
can vary depending upon several factors [55, 68]. Lastly, low CD4
count is a common finding, with documented suppression for up
to 1-year or longer post infusion [14, 15, 17]. However, some
studies showed that, although low CD4 lymphocyte count was
common, it was not associated with increased risk of severe
infection [15].

Hypogammaglobulinemia is a known sequelae of CAR T-cell
therapy due to depletion of CD19 + B lymphocytes and BCMA +/-
CD19 + plasma cells. The incidence of hypogammaglobulinemia
varies between 20 and 90% [2–4, 22, 56, 69–71]. Up to 40% of
patients who undergo CAR T-cell therapy have pre-existing
hypogammaglobulinemia secondary to prior treatments. CAR
T-cells can further worsen immunoglobulin deficit both qualitatively
and quantitatively. The severity and duration of hypogammaglob-
ulinemia have been closely correlated with the degree and
duration of B lymphocyte/plasma cell cell depletion. However, the real
incidence, duration, and severity of hypogammaglobulinemia can
carry according to practice patterns of immunoglobulin replacement
therapy. Moreover, the kinetics of IgG levels may also differ between
underlying diagnosis and targets of CAR T-cells. In one report,
patients with B-ALL had the most significant change in IgG levels
between pre- and post-CAR T-cell therapy compared to patients
with DLBCL and CLL [13, 72]. To date, there is also evidence
indicating that total IgG may not reflect infection risk. Hill and
colleagues demonstrated that specific IgG level to certain organ-
isms can be independent and not correlate with total IgG level.
The changes in pathogen-specific IgG level can vary among different
pathogens with data suggesting that viral hepatitis, encapsulated
bacteria, and Bordetella pertussis are most affected, whereas other
viral or bacterial-specific antibodies are preserved (i.e., measles) [72].
Bhoj et al. showed that CD19 negative long-lived plasma cells might
be preserved after CD19 CAR T-cell therapy and might explain the
persistence of pre-existing humoral immunity against certain
organisms in CD19 CAR T-cell recipients [73].

Lastly, BCMA-targeted CAR T-cells may also have more negative
effect on post-CAR T pathogen-specific antibody level compared

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to CD19 CAR T-cell products [57]. Joshyula et al. reported a cohort of 32R/R MM patients treated with BCMA CAR T-cell and observed that most patients had low IgG level and lost measles-specific IgG [33]. Besides the quantitative effect on IgG level, CAR T-cells against different targets also result in different impacts on the diversity of IgG. Patients with RR multiple myeloma who were treated with BCMA-targeted CAR T-cells also lost the diversity of immunoglobulin against microorganism [74]. These patients can have prolonged and profound hypogammaglobulinemia due to the depletion of all subsets of plasma cell populations.

ANTIMICROBIAL PROPHYLAXIS AND IMMUNOGLOBULIN REPLACEMENT IN CAR T-CELL THERAPY

There are several professional organizations and expert opinion statements that provide recommendations on prophylactic and management strategies for infection post-CAR T-cell therapy, mostly adopted from practice guidelines used in hematopoietic stem cell transplant recipients [20, 75, 76]. Here, we highlight approaches for CD19 targeted CAR T-cell therapy.

1. **Antibacterial prophylaxis:** As risk of bacterial infection inversely correlates with the degree and duration of neutropenia, most guidelines recommend initiating anti-bacterial prophylaxis during the severe neutropenia period with absolute neutrophil counts (ANC) lower than 0.5 × 10^9/L and continue until ANC stays sustained above this level. Fluoroquinolones (i.e., levofloxacin) are most commonly used, but extended-spectrum beta-lactam antibiotics (i.e., amoxicillin/clavulanic acid) or nonabsorbable antibiotics (i.e., rifaximin) may be a reasonable alternative depending upon the antimicrobial sensitivity pattern in each region, allergy profiles of the patients, and practice patterns at each center.

   In addition to antibiotic prophylaxis, the role of granulocyte colony-stimulating factors to decrease risk of bacterial infection by shortening the duration of neutropenia has been a debated topic. There were some concerns that G-CSF might affect CAR T-cell response or worsen CRS or ICANS via the activation of myeloid-related cytokines [77, 78]. Overall, the data on the G-CSF are still conflicting, and some studies did not support this concern or suggested that G-CSF administration after the acute phase of CAR T-cell may shorten the duration of neutropenia and decrease the risk of infection in CAR T-cell recipients [79–82]. However, the finite role and effect of G-CSF require further studies. Currently, most experts recommend considering G-CSF in patients with prolonged neutropenia [83, 84]. The administration of G-CSF for prolonged cytopenia beyond 14–21 days after CAR T-cell infusion appeared safe and did not exacerbate CRS [79, 85].

2. **Antiviral prophylaxis:** Prophylactic acyclovir is recommended from the initiation of LD chemotherapy for herpes viral prophylaxis. The duration of antiviral prophylaxis is varied between institutions. Some institutions adopt fixed duration approach for at least 3–6 months after CAR T-cell therapy [17]. However, delayed herpetic and zoster viral reactivation has been reported [14]. Thus, most experts now recommend maintaining acyclovir prophylaxis for an extended period or adopt CD4 guided approach to continue anti-viral prophylaxis until CD4 lymphocyte counts are higher than 200/μL.

   Patients who are hepatitis B carriers (HBs Ag positive) or have previous history of hepatitis B infection (HBs Ag negative, Anti-HBc Ab IgG positive) should receive prophylaxis with entecavir for at least 6 months along with surveillance by checking liver function test or HBV DNA. Patients with chronic active hepatitis B (HBsAg positive) with HBe Ag have a higher risk of reactivation than patients with anti-HBc Ab but negative HBs Ag with some fatal cases being reported [86, 87]. Patients with chronic hepatitis B infection should have suppressed HBV DNA level before undergoing CAR T-cell therapy. With entecavir prophylaxis and close surveillance, CAR T-cell therapy is feasible and safe in patients with evidence of previous or chronic hepatitis B infection [88–91].

   As SARS-CoV-2 virus has emerged as a major infectious disease threat over the past 2 years, patients with hematologic malignancies receiving active anti-cancer treatments are at risk of developing severe infection [92]. Although there is no evidence for antiviral prophylaxis for SARS-CoV-2 infections, many centers are using pre-exposure prophylaxis with long-acting monoclonal antibody tixagevimab/cilgavimab to prevent the occurrence of symptomatic infection [93]. A recent report from MSK supports the use of 300 mg dose, as recommended by the US FDA, but also highlights the fact that the antibody appears less effective against the emerging Omicron variants [94].

3. **Antifungal prophylaxis:** Although fungal infection is uncommon in patients undergoing CD19 CAR T-cell therapy, antifungal prophylaxis should be considered in some patients with prolonged cytopenia or prolonged systemic corticosteroid treatment for CAR T-cell-associated adverse events [20, 95]. In patients who are not high risk for fungal infection and do not have previous history of active fungal infection, fluconazole should be continued until the resolution of neutropenia. However, in patients with prolonged neutropenia, a history of prior mold infection, or higher grade of CAR T-cell associated complications requiring intensive immunosuppressants, later generation of mold active azoles and infectious disease consultation may be indicated [20, 75, 95].

   For prophylaxis of pneumocystis infection, most available guidelines recommend trimethoprim/sulfamethoxazole to be initiated at around 1 month post-CAR T infusion if blood count recovery allows, otherwise less myelosuppressive alternatives such as inhaled pentamidine, dapsone or atovaquone should be considered. Prophylaxis against pneumocystis infection is recommended by most experts to be extended until recovery of CD4 above 200/μL due to potential infection in early discontinuation reported by some previous studies [14, 17].

4. **Immunoglobulin replacement:** Data on immunoglobulin replacement in CAR T-cell therapy is extrapolated from patients with hematologic malignancy who receive anti-CD20 monoclonal antibody and patients who undergo allogeneic HSCT [96, 97, 99]. Therefore, it is unclear if IVIG replacement alters the overall post-CAR T-cell IgG level or improves survival outcomes [96, 100]. Wudhikarn and colleagues showed that IVIG replacement had no correlation with the incidence of infection in patients treated with CD19 CAR T-cells [17]. Similarly, Baird et al. reported no difference in IgG level during post-CAR T-cell follow-up irrespective of IVIG replacement [14]. As described earlier, the effect of CAR T-cell on humoral immunity against certain microorganisms is highly different therefore the benefit of IVIG replacement on the prevention of certain types of infection may not be equal. Practice patterns around IVIG replacement can vary widely among practicing providers and institutions. Most guidelines and recommendations from expert opinion suggest giving IVIG replacement to patients with IgG level below 400 mg/dL or 400–600 mg/dL who have history of recurrent infection [20, 74, 101, 102].
| Killed/inactivated vaccines\(^a\) | Pre-CAR | 3 m | 4 m | 6 m | 6 + m | 7 + m | 8 + m | 10 + m | 12 + m | 18 + m | 20 + m | 22 + m | 24 + m | 26 + m | 27 + m | Time between doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SARS-CoV-2 vaccine (mRNA-based) | X | X | X | X | | | | | | | | | | | | |
| Influenza (inactivated) | X | X | | | | | | | | | | | | | | |
| Pneumococcal conjugate | Titer | X | Titer\(^c\) | X | X | | | | | | | | | | | 1–2 m |
| Pneumococcal polysaccharide | Titer | Titer\(^c\) | X | Titer\(^c\) | | | | | | | | | | | | |
| Diphtheria/Tetanus/acellular Pertussis | Titer | X | Titer\(^c\) | X | X | Titer\(^c\) | | | | | | | | | | 1–2 m |
| Hemophilus influenza type B | Titer | X | Titer\(^c\) | X | X | Titer\(^c\) | | | | | | | | | | 1–2 m |
| Hepatitis A | Titer | X | Titer\(^c\) | X | X | Titer\(^c\) | | | | | | | | | | 6 m |
| Hepatitis B | Titer | X | Titer\(^c\) | X | X | Titer\(^c\) | | | | | | | | | | 2 m |

**Live and non-live adjuvant Vaccines\(^b\)**

| Live and non-live adjuvant Vaccines\(^b\) | Pre-CAR | 6 m | 6 + m | 7 + m | 8 + m | 10 + m | 12 + m | 18 + m | 20 + m | 22 + m | 24 + m | 26 + m | 27 + m | Time between doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MMR | | X | X | Titer\(^c\) | | | | | | | | | | | | |
| Varicella-Zoster (live); Seronegative | | X | X | | | | | | | | | | | | 1 m |
| Varicella-Zoster (non-live adjuvant) in VZV seropositive patients; >50 years | | X | X | | | | | | | | | | | | 1–2 m |

\(^a\)For inactivated virus vaccines, vaccines should be given at least 2 months post last dose of IVIG.

\(^b\)For killed attenuated or non-live adjuvant vaccines will not be given until 1-year post-CAR T-cells (and at least 2 years post-HSCT if patients had HSCT prior to CAR T-cell therapy), at least 5 months after last dose of IVIG, absolute CD4 count >200/µL.

\(^c\)If patients do not develop response after a given dose of vaccination, additional vaccination should be deferred until there is evidence of immune reconstitutions: Detectable serum IgA, and CD19 B cell count >20/µL and CD4 + T cell count >200/µL (all of which should be fulfilled).
later phases. Duration of B cell aplasia, hypogammaglobulinemia, and CD4 lymphopenia can be widely different and may not correlate to each other. Most data indicate that CD4 lymphocyte will gradually recover after 3–6 months after CAR T-cell therapy but in certain occasions can be delayed and suppressed over 12 months. However, factors that determine the ability to mount immune response to vaccination after CAR T-cell therapy are not well understood. In a recent study, neither B cell aplasia or low IgG predicted vaccine immunogenicity and thus should not preclude vaccination after CAR T-cells [58]. While patients treated with CAR T-cells had lower rate of seroprotection after vaccinations, some patients could develop adequate immune responses. In addition, a proportion of patients who had vaccination pre-CAR-T cell therapy developed antibody response to vaccines after post-CAR-T cell boost or had persistent seroprotective antibody level for up to 3 months post-CAR T-cell therapy [72].

Most professional societies including ASH, ASTCT, and EBMT issued guidelines adopted from recommendations in alloHCT [103, 104]. In general, it is recommended to start immunization with inactivated/killed pathogen vaccines after 3–6 months and consider giving live attenuated virus vaccine at least 12 months post-CAR T-cell (or until CD4 count >200/μL), respectively. Physicians may incorporate the pathogen-specific IgG level and post-immunization immune response to guide decision for vaccination in these patients.

Regarding SARS-CoV-2 vaccine, the current guidelines recommended that patients who are scheduled to undergo CAR T-cell therapy should complete primary series of SARS-CoV-2 vaccines at least two weeks before the initiation of LD chemotherapy to allow memory T cell formation if feasible. In addition, patients who had COVID-19 vaccination before CAR T-cell therapy also should have repeated COVID-19 vaccination series [105]. Currently, ASH/ASTCT currently recommends a complete series of mRNA-based COVID19 vaccines including a booster starting at 3 months after CAR T-cell therapy [106]. The primary series of COVID-19 vaccination could be either 3 doses of mRNA-based vaccine or a dose of the adenovirus vector-based vaccine followed by a second dose of the mRNA-based vaccine. The booster dose could be given ~2–3 months after the primary vaccination according to the most recently updated guideline of COVID-19 vaccination for patients with moderate or severe immunocompromised states. Data on the response to COVID-19 vaccination are conflicting. Abid et al. reported the overall response rate of 31% to SARS-CoV-2 vaccine in CAR-T-cell therapy recipients [107]. Dhakal et al. also reported a single-center experience showing a low rate of humoral immune response (21%) after COVID-19 vaccination in patients treated with CD19 CAR T-cells [108]. However, in another study, Tamari et al. reported that 77% of patients achieved positive neutralization activity 3 months after COVID-19 vaccination [109]. Jarisch et al. also demonstrated a robust T cell response, especially in CD4 lymphocyte subset, in eight lymphoma patients who received CD19 CAR T-cells [110]. Moreover, Parvathaneni et al. showed that despite lower humoral response to SAR-CoV2 vaccines, spike-specific T cell response to mRNA-based vaccines (BNT162b2 and mRNA-1273) in 12 patients treated with CD19 CAR T-cells was comparable to healthy control [111]. Further larger prospective studies are required to help physicians better understand and provide appropriate vaccination to CAR T-cell recipients. Table 3 summarizes the recommendation for vaccination in patients treated with CAR T-cells [20].

**CONCLUSION**

Infectious complications are common in patients who undergo CAR T-cell therapy. As CAR T-cell therapy increasingly becomes a critical treatment component of hematologic malignancy, better understanding of the natural history of infection and the kinetics of immune reconstitution in these patients will provide treating physicians more insight to provide proper management for the patients.

**DATA AVAILABILITY**

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Author Contributions
KW generated the concept of the study, conducted the literature search, reviewed the literature, and draft the initial manuscript. MAP contributed to writing the manuscript and provided feedback on the manuscript. All authors reviewed and approved the final version of the manuscript.

Competing Interests
M-AP reports honoraria from Abbvie, Allovir, Astellas, Bristol-Myers Squibb, Celgene, Equillum, Exevir, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Novartis, Nektar Therapeutics, Omeros, OcsaBio, Takeda, and VectivBio AG, Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, Sellas Life Sciences, and Servier, and the scientific advisory board of Neximmune. He has ownership interests in Neximmune and Omeros. He has received institutional research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis. KW declares no relevant conflict of interest.

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