Tocilizumab administration in cytokine release syndrome is associated with hypofibrinogenemia after chimeric antigen receptor T-cell therapy for hematologic malignancies

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy causes serious side effects including cytokine release syndrome (CRS). CRS-related coagulopathy is associated with hypofibrinogenemia that has up to now been considered the result of disseminated intravascular coagulation (DIC) and liver dysfunction. We investigated the incidence and risk factors for hypofibrinogenemia in 41 consecutive adult patients with hematologic malignancies (median age 69 years, range 38-83 years) receiving CAR T-cell therapy between January 2020 and May 2023 at the University Medical Center Regensburg. CRS occurred in 93% of patients and was accompanied by hypofibrinogenemia already from CRS grade 1. Yet DIC and liver dysfunction mainly occurred in severe CRS (≥ grade 3). After an initial increase during CRS, fibrinogen levels dropped after administration of tocilizumab in a dose-dependent manner (r = -0.44, *P*=0.004). In contrast, patients who did not receive tocilizumab had increased fibrinogen levels. Logistic regression analysis identified tocilizumab as an independent risk factor for hypofibrinogenemia (odds ratio = 486, *P*<0.001). We thus hypothesize that fibrinogen synthesis in CRS is up-regulated in an interleukin-6-dependent acute phase reaction compensating for CRS-induced consumption of coagulation factors. Tocilizumab inhibits fibrinogen upregulation resulting in prolonged hypofibrinogenemia. These observations provide novel insights into the pathophysiology of hypofibrinogenemia following CAR T-cell therapy, and emphasize the need for close fibrinogen monitoring after tocilizumab treatment of CRS.

Introduction

The adoptive transfer of chimeric antigen receptor (CAR)-modified T cells is a breakthrough for the treatment of relapsed/refractory lymphoma,[1,2] multiple myeloma,[3] and acute lymphoblastic leukemia,[4] and is a subject of research in different solid tumors.[5] Its efficacy arises from a tumor antigen-directed response of gene-modified immune cells at the expense of significant toxicity and adverse events, primarily cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Current CAR T-cell therapies are associated with CRS and ICANS rates of up to 95%[6] and 64%[7] (any grade), respectively, and necessitate frequent intensive care unit (ICU) admissions.

Cytokine release syndrome is characterized by a systemic inflammatory response due to activation of large numbers of CAR T cells, resulting in a cytokine storm driven by interferon γ (IFNγ), tumor necrosis factor α (TNFα), interleukin-(IL-)2 and IL-6 that occurs within hours to days after cell infusion.[8] Subsequently, bystander immune cells augment the proinflammatory cascade, and perpetuate the activation and injury of endothelial cells with subsequent coagulation imbalance and capillary leakage.[9,10] Clinical manifestations of CRS involve fever, hypotension, hypoxia, and progressive organ failure.[8,11,12] Management of CRS is based on clinical symptoms and severity, and includes symptomatic therapy, the administration of the IL-6 receptor antagonist tocilizumab, and, ultimately, the

use of corticosteroids and other immunosuppressants.[13,14] Refractory CRS, as well as high ferritin levels combined with severe multiorgan dysfunction[14,15] and consumptive coagulopathy/disseminated intravascular coagulation (DIC),[16,17] suggest a transition to immune-effector cell-associated hemophagocytic lymphohistiocytosis (HLH)-like syndrome (IEC-HS).

Overall, abnormal coagulation parameters are observed in approximately every second patient after CAR T-cell therapy. Thereby, the severity of coagulopathy correlates with the severity of CRS.[18-20] Of note, hypofibrinogenemia is reported in up to 25% of patients treated with CAR T-cell therapy and is disproportionate compared with other coagulation parameters that are less frequently affected.[21,22] The reasons are not sufficiently understood, but HLH-associated secondary fibrinolysis by consumption (i.e., DIC) and primary fibrinolysis by mediators such as plasminogen derived from CRS-promoting lymphocytes and monocytes are discussed.[21,23] These hypotheses are supported by increased levels of endothelial activation markers like angiopoietin-2 and von Willebrand factor in the serum of patients with severe CRS.[24] Nevertheless, considering the high frequency of patients with hypofibrinogenemia in comparison to the lower rate of severe CRS or IEC-HS, numerous cases of hypofibrinogenemia remain unexplained.

We thus examined the incidence, severity, time course, and potential risk factors for hypofibrinogenemia in patients receiving CAR T-cell therapy at the University Medical Center Regensburg between 2020 and 2023.

Methods

Patients

All consecutive 41 patients (pts) who received CAR T-cell therapy for hematologic malignancies between January 2020 and May 2023 at the Department of Internal Medicine III of the University Medical Center Regensburg (Regensburg, Germany) were included in the analysis. Data on the disease course and treatment were assessed during inpatient therapy and regular outpatient visits. Patient comorbidities were evaluated using the Charlson Comorbidity Index.[25] The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the local ethics committee (N. 23-3429-104).

Laboratory analysis

Blood samples were routinely analyzed at the Department of Clinical Chemistry of the University Medical Center Regensburg according to clinical practice, and blood examinations were adjusted as needed. Methods and devices for the determination of laboratory values are presented in the *Online Supplementary Appendix* and *Online Supplementary Table S1*.

Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome grading and treatment

Cytokine release syndrome and ICANS assessments were regularly performed during the inpatient stay and at outpatient visits. Severity was graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria[26] and treatment followed the recommendation of the European Society for Blood and Marrow Transplantation.[13] Coagulopathy and hypofibrinogenemia were classified according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0. Substitution of vitamin K or coagulation factors (fibrinogen, antithrombin-III [AT-III], fresh frozen plasma [FFP]) was based on laboratory results, clinical symptoms, and/or in case of bleeding complications.

Statistical analysis

Statistical analysis was performed using RStudio version 2023.06.2+561 (Posit, Boston, MA, USA) and R version 4.3.1 (The R Foundation, Vienna, Austria). The level of significance was set at a two-sided $P \leq 0.05$ with 95% confidence intervals. Incidence is reported as incidence proportion calculated as new cases during the observation period divided by the total number of patients (N=41). Data are depicted as box plots (Tukey), and groups were compared by Kruskal-Wallis test for interval scaled and Pearson's χ^2 test for categorical data. Pearson and Spearman correlation coefficients were calculated depending on the distribution and linearity of the data. Progression-free survival (PFS) was defined as the time of CAR T-cell treatment and progression of the underlying disease or death from any reason, and is presented as a Kaplan-Meier curve with differences between groups calculated using the log-rank test. Multivariate logistic regression analysis was performed with the glm() function of R stats package version 4.3.1.

Results

Patients' characteristics

We analyzed 41 consecutive patients (Table 1) with a median age of 69 years (range, 38-83 years) and equal gender distribution (54% female). Most patients received CAR T cells for the treatment of diffuse large B-cell lymphoma (73%); the most common CAR T-cell products were tisagenlecleucel and axicabtagene ciloleucel. The majority of patients (93%) developed CRS, which was high-grade (grades 3 and 4) in 13%. One-third of patients developed ICANS, two of those grade 4. For the treatment of CRS and ICANS, 71% of patients received tocilizumab and 34% high-dose corticosteroids (i.e., dexamethasone, methylprednisolone).

Hypofibrinogenemia is common and persistent after chimeric antigen receptor T-cell therapy

Fibrinogen levels prior to CAR T-cell therapy were above the lower limit of normal (LLN) in all but one patient. Hy-

pofibrinogenemia occurred in 27 patients (66%) after CAR T-cell therapy (new onset), which was severe (CTCAE grade 3 or 4) in 11 patients (41%) and associated with the onset of CRS in all cases. While hypofibrinogenemia was seen in only a few patients with CRS grade 1 (5/13 pts; 38%), the majority (22/25 pts; 88%) developed hypofibrinogenemia in CRS ≥grade 2. The severity increased with rising CRS grades (Figure 1A), except for one patient with grade 4 CRS who received coagulation factor substitution in the ICU but who soon died of CRS.

One patient developed bleeding (CTCAE grade 1), one developed thrombosis (CTCAE grade 3), and one developed both (bleeding CTCAE grade 3 + thrombosis CTCAE grade 2). Fibrinogen substitution was required in 30% of patients (8/27) with a median cumulative dose of 3 g (range, 1-9 g). Vitamin K and coagulation factors were substituted in 17 patients (vitamin K, 14 pts; AT-III, 7 pts; and FFP, 4 pts). Median day to resolution of hypofibrinogenemia was 44 days (range, 9-181 days) after CAR T-cell therapy and 20 days (range, 1-171 days) after minimum fibrinogen levels, whereas 6/27 patients had not exceeded LLN at the time of last follow-up. Patients with and without hypofibrinogenemia exhibited a comparable PFS (P=0.4) (*Online Supplementary Figure S1*).

Consumptive coagulopathy / disseminated intravascular coagulation and hepatopathy are associated with high-grade cytokine release syndrome

Since fibrinogen levels were impaired in a large fraction of patients from CRS grade 1 (*Online Supplementary Table S2*), we further investigated global coagulation parameters. D-dimers indicating increased fibrinolysis were significantly elevated with increasing CRS grades (P=0.004) (Figure 1B) and negatively correlated with fibrinogen levels (R = -0.57, P<0.001) (Figure 1C). Platelet counts, international normalized ratio (INR), and partial thromboplastin time (PTT) were only impaired for high-grade (i.e., grades 3 and 4) CRS (Figure 1D-F).

Consumptive coagulopathy / DIC is considered a main reason for hypofibrinogenemia after CAR T-cell therapy. Further parameters besides hypofibrinogenemia and elevated D-dimers indicating the occurrence of DIC (i.e., thrombopenia, increased INR) are summarized in the DIC score.[27] A positive DIC score (≥ 5 points) was observed in a minority of patients with CRS grade 1 (15%) and grade 2 (40%), but in all patients with high-grade CRS.

Liver dysfunction primarily occurs in high-grade cytokine release syndrome

Another hypothesis for hypofibrinogenemia after CAR T-cell therapy is the impairment of liver synthesis due to hepatopathy. Gamma-glutamyltransferase (gGT) levels were only slightly increased in low-grade (i.e., grades 1 and 2), but significantly increased in high-grade CRS (P=0.0093) (Figure 2A), whereas alanine transaminase (ALT) was only increased in CRS grade 4 (P=0.15) (Figure 2B). Liver injury translated into reduced synthesis parameters (cholinesterase [CHE]) only in patients with CRS grade 4 (P=0.65) (Figure 2C). Albumin, an inflammation sensitive liver synthesis parameter, decreased throughout all CRS grades (P=0.0075) (Figure 2D). Taken together, non-functional liver injury occurred early and depended on the severity of CRS, but clinically relevant liver dysfunction only occurred in advanced CRS.

Table 1. Patients' characteristics.

Parameter	N (%)
Total	41 (100)
Age in years (range)	69 (38-83)
Female sex	22 (54)
Disease	
High-grade B-NHL	30 (73)
Primary	21 (70)
Secondary transformed	9 (30)
Multiple myeloma	5 (12)
Follicular lymphoma	3 (7)
Mantle cell lymphoma	2 (5)
Acute lymphoblastic leukemia	1 (2)
Bulky disease	13 (32)
CAR T-cell product (target)	
Tisagenlecleucel (CD19)	18 (44)
Axicabtagene ciloleucel (CD19)	14 (34)
Idecabtagene vicleucel (BCMA)	5 (12)
Brexucabtagene autoleucel (CD19)	3 (7)
Experimental CAR (CD19/CD20)	1 (2)
CRS, total	38 (93)
Grade 1	13 (34)
Grade 2	20 (53)
Grade 3	3 (8)
Grade 4	2 (5)
ICANS, total	12 (29)
Grade 1	7 (59)
Grade 2	3 (25)
Grade 3	0
Grade 4	2 (17)
Tocilizumab administration	29 (71)
Corticosteroid administration	14 (34)

B-NHL: B-cell non-Hodgkin lymphoma; CAR: chimeric antigen receptor; BCMA: B-cell maturation antigen; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

Immune-effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome is a rare complication after chimeric antigen receptor T-cell therapy

The HLH-like syndrome (IEC-HS) is another life-threatening complication associated with hypofibrinogenemia. According to the ASTCT committee on cellular therapy, diagnostic criteria include hypofibrinogenemia with simultaneously (i.e., within 72 hours) elevated ferritin (>2-fold baseline / upper limit of normal [ULN]) and hepatic transaminase

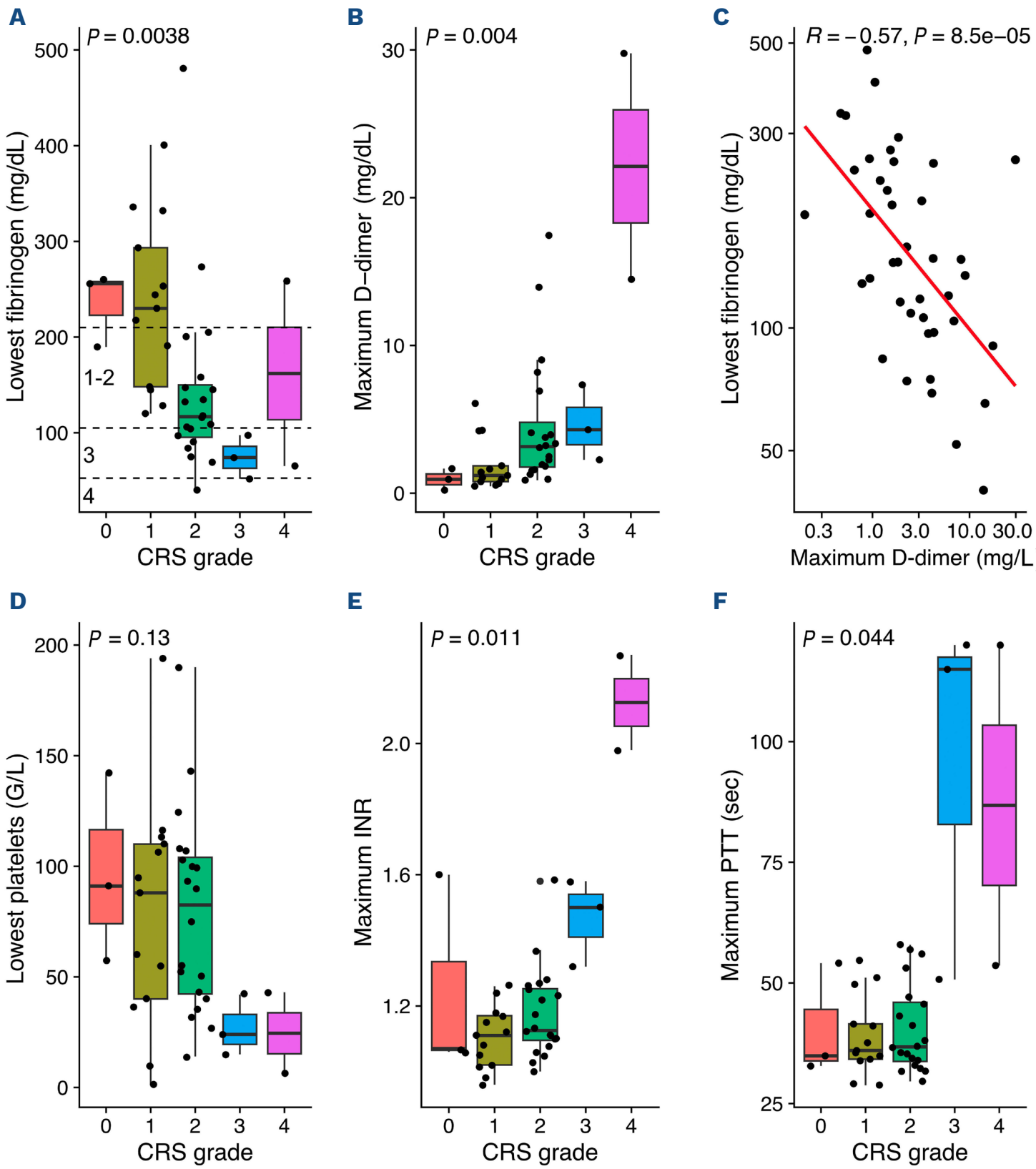

Figure 1. Hypofibrinogenemia occurs in all grades of cytokine release syndrome, whereas disseminated intravascular coagulation is characteristic only for high-grade cytokine release syndrome. (A) Fibrinogen, (B) D-dimers, (D) platelet, (E) international normalized ratio (INR), and (F) partial thromboplastin time (PTT) values are altered in cytokine release syndrome (CRS) patients, but only fibrinogen levels are already decreased in low-grade CRS. (C) Fibrinogen negatively correlates with increased D-dimers. Dashed lines represent Common Terminology Criteria for Adverse Events grades in (A). sec: second.

levels (>5-fold baseline / ULN).[15] In our cohort, 4 patients (10%) with CRS grades 2 (N=3) and 4 (N=1) met the criteria. These individuals exhibited hypofibrinogenemia with a median onset of eight days (range, 6-13 days) after their initial diagnosis of CRS. Only 2 patients received specific IEC-HS treatment (patient 1: anakinra, cyclophosphamide, methylprednisolone; patient 2: dexamethasone). Thus, IEC-HS likely contributed to hypofibrinogenemia in only a fraction of patients. However, the high frequency of hypofibrinogenemia (observed in 66% of all patients) cannot be solely attributed to the limited number of IEC-HS cases in our cohort.

Administration of tocilizumab is associated with persistent hypofibrinogenemia

A large fraction of patients already developed hypofibrinogenemia in low-grade CRS (grades 1 and 2: 23/33 pts; 70%), whereas consumption and reduced liver synthesis occurred only in high-grade CRS. Thus, further mechanisms seem to contribute. A comparison of patients with

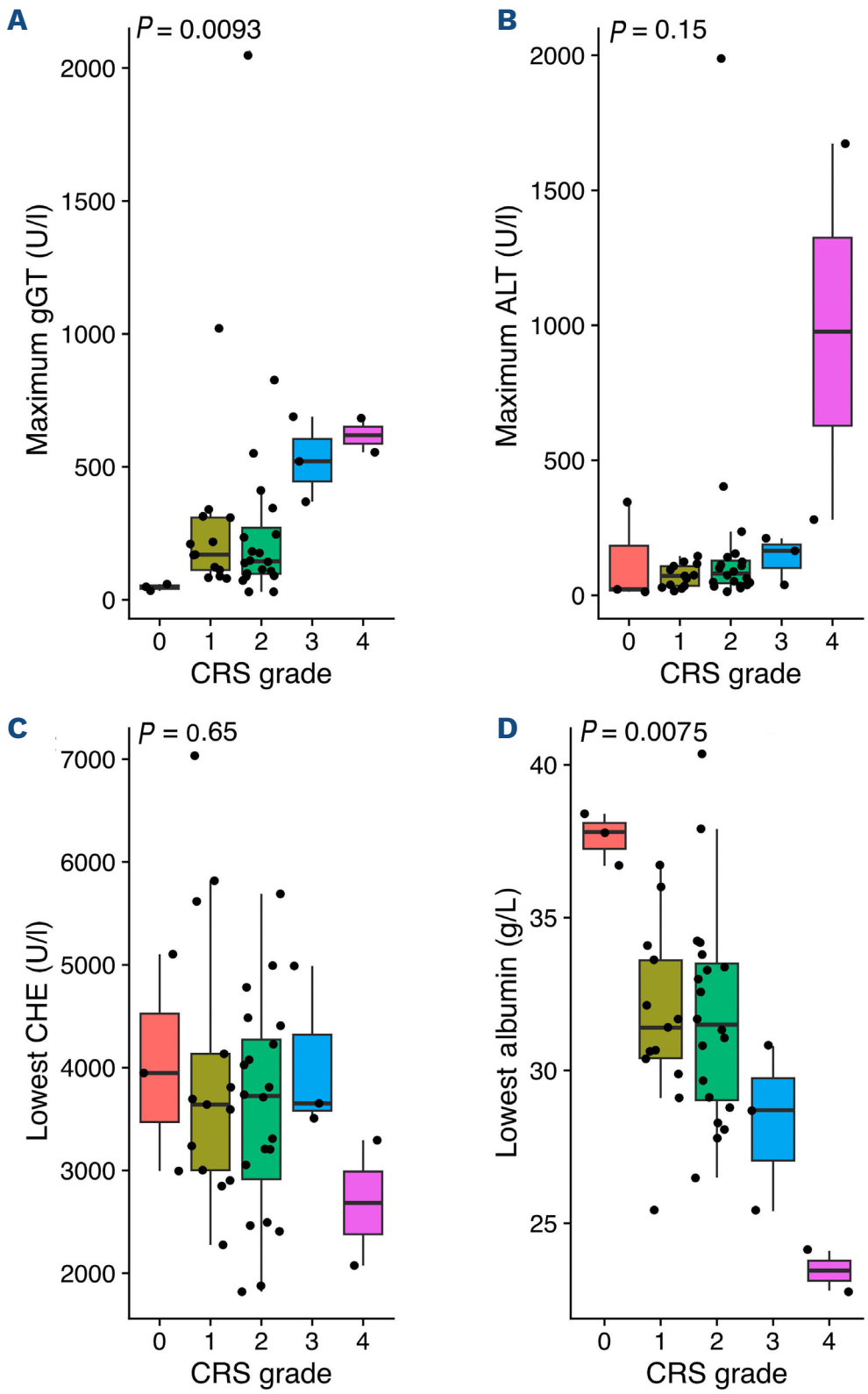

Figure 2. Impairment of liver synthesis characterizes high-, but not low-grade cytokine release syndrome. (A-C) Gamma glutamyltransferase (gGT), alanine transaminase (ALT), and choline esterase (CHE) are affected in high-grade cytokine release syndrome (CRS), while (D) albumin, a sensitive marker for inflammation and liver synthesis, steadily decreases with increasing CRS grades.

CRS grades 1 and 2 who developed hypofibrinogenemia *versus* patients without hypofibrinogenemia revealed that the main difference between both groups was the use of the IL-6 receptor antagonist tocilizumab for the treatment of CRS (P<0.001) (Figure 3A). Of 29 patients treated with tocilizumab for any grade CRS, 27 (93%) developed hypofibrinogenemia (below LLN) and the lowest absolute levels were observed in CRS grades ≥2. In contrast, patients who did not receive tocilizumab treatment did not develop hypofibrinogenemia (Figure 3A). The median time to onset of hypofibrinogenemia after the first tocilizumab administration was six days (range, 2-27). *Online Supplementary Figure S2* shows representative fibrinogen curves for patients upon treatment and *Online Supplementary Table S2* presents patients' characteristics categorized by CRS grades and use of tocilizumab. Interestingly, patients who did not receive tocilizumab had a sustained increase in fibrinogen levels throughout the course of CRS, while tocilizumab-treated patients showed a sharp decline in fibrinogen levels after tocilizumab administration.

We further investigated the impact of cumulative tocilizumab dosage. We found a significant correlation between this dosage and the extent of fibrinogen decrease (R = -0.44, P=0.004) (Figure 3B) as well as the time required for fibrinogen to recover from the lowest levels to normal (R = 0.43, P=0.05) (Figure 3C). On average, mild to moderate hypofibrinogenemia (CTCAE grades 1-2) developed after 1-2 doses of tocilizumab, whereas severe hypofibrinogenemia (CTCAE grades 3-4) occurred after 3 or more doses (P<0.001) (Figure 3D). There was also a notable correlation between

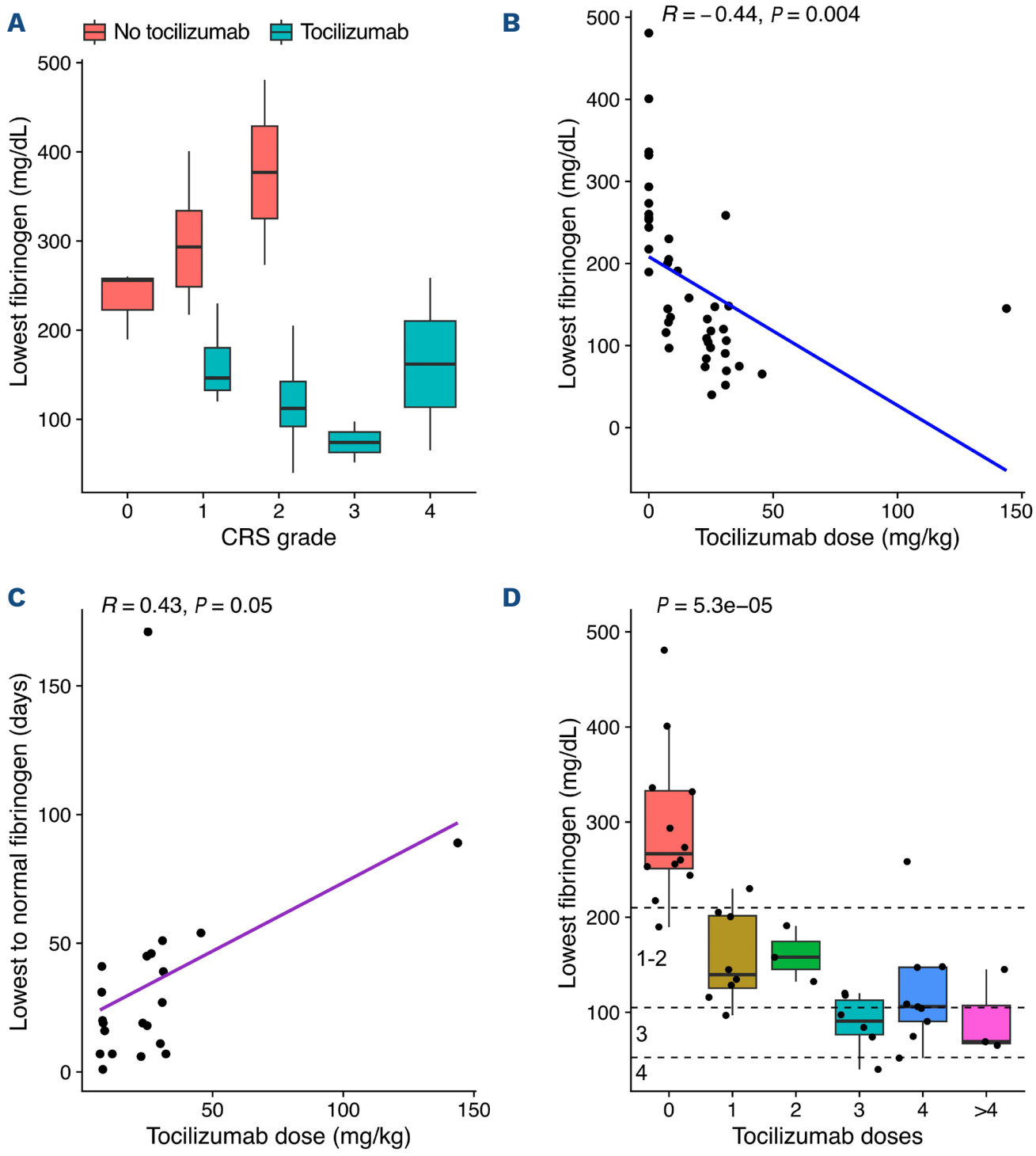

Figure 3. Hypofibrinogenemia is associated with tocilizumab administration. (A) Lowest observed fibrinogen levels after chimeric antigen receptor (CAR) T-cell therapy decrease with increasing CRS grade in patients who received tocilizumab (turquoise), whereas they increase in patients who did not receive tocizliumab (red). (B, C) Cumulative tocilizumab dosage significantly correlates with the minimum fibrinogen levels and the duration of fibrinogen recovery from lowest to normal levels after CAR T-cell therapy. (D) Average severity of hypofibrinogenemia is mild to moderate after ≤2 doses, and severe after ≥3 doses. Dotted, horizontal lines represent severity levels according to Common Terminology Criteria for Adverse Events.

the number of tocilizumab administrations and both the severity (R = 0.44, *P*=0.004) (*Online Supplementary Figure S3A*) and duration (R = 0.47, *P*=0.03) (*Online Supplementary Figure S3B)* of hypofibrinogenemia. Furthermore, the overall duration of tocilizumab treatment (from the first to the last day of administration) inversely correlated with the lowest (nadir) fibrinogen levels (R = -0.45, *P*=0.015) (*Online Supplementary Figure S3C*).

Next, we performed a multifactorial regression model including the known risk factors and possible confounders for CAR T-cell-associated coagulopathy as well as tocilizumab use (i.e., age, bulky disease, use of CD28 co-stimulatory CAR T cells, maximum D-dimer levels, minimum CHE, lymphodepletion regimen, and Charlson Comorbidity Index). This regression model confirmed tocilizumab as an independent risk factor for the development of hypofibrinogenemia (*P*<0.001, OR = 486) (*Online Supplementary Table S3*).

Discussion

Here, we describe the incidence, severity, and risk factors for hypofibrinogenemia following CAR T-cell therapy. Previous studies demonstrated a disproportionate incidence

of severe or even life-threatening hypofibrinogenemia in up to 25% of patients with CRS.[21,22] In our cohort, 66% of patients developed any grade and 27% CTCAE grade ≥3 hypofibrinogenemia, in line with previous reports. Although most patients had low grade (≤2) CRS during inpatient monitoring, and no patient showed signs of CRS at discharge, surprisingly, fibrinogen levels did not normalize on average until day 44 after CAR T-cell therapy.

Thus far, hypofibrinogenemia had been attributed to consumptive coagulopathy due to endothelial injury and primary hyperfibrinolysis caused by CRS.[21,23] We also found a positive association between higher CRS grades and D-dimers, and a direct correlation of D-dimers with the severity of hypofibrinogenemia. Yet DIC (representing a generalized form of coagulation failure) and liver dysfunction were mostly observed in high-grade (≥3) CRS. Coagulation failure accompanied by hypofibrinogenemia is also a key characteristic of IEC-HS, a syndrome driven by a proinflammatory feedback loop between CAR T cells and macrophages causing systemic inflammation and organ damage. Notably, it has been suggested that tocilizumab administration might even promote HLH-like toxicity by increasing free IL-18 levels.[28] Although this condition is associated with coagulation failure, in our study, only a small fraction (10%) of patients met the recently proposed criteria for IEC-HS.[15]

Given the high incidence and long duration of hypofibrinogenemia even in early CRS stages, and the disproportionate rate of hypofibrinogenemia compared to other features of coagulation failure (i.e., thrombocytopenia, increased PTT and INR), we suspected another cause of inappropriate fibrinogen supply. Fibrinogen is a protein that is up-regulated during the acute phase reaction (APR).[29] The APR is a systemic cascade initiated in response to inflammation fueled by a variety of cytokines, particularly IL-6.[30] The binding of IL-6 to hepatocytes, and subsequent signaling through signal transducer and activator of transcription 3 (STAT3) and the IL-6 responsive element, have been identified as the major upregulators of fibrinogen synthesis, potentiated by glucocorticoids and counteracted by IL-1β.[31] Similar findings were described in a case report demonstrating a significant connection between IL-6 signaling and fibrinogen levels.[32] Besides its importance for acute phase reactions, IL-6 plays a pivotal role in the pathogenesis of CRS. Hence, blockade of the IL-6 receptor by the monoclonal antibody tocilizumab has been established as the first-line treatment for CRS.[11,13] Tocilizumab has a concentration-dependent half-life of approximately ten days and effectively suppresses the secretion of liver-derived acute phase proteins, such as CRP, even at very low plasma concentrations.[33] Administration of tocilizumab for COVID-19 disease and rheumatoid arthritis was associated with rare cases of hypofibrinogenemia.[34-36] In contrast, more

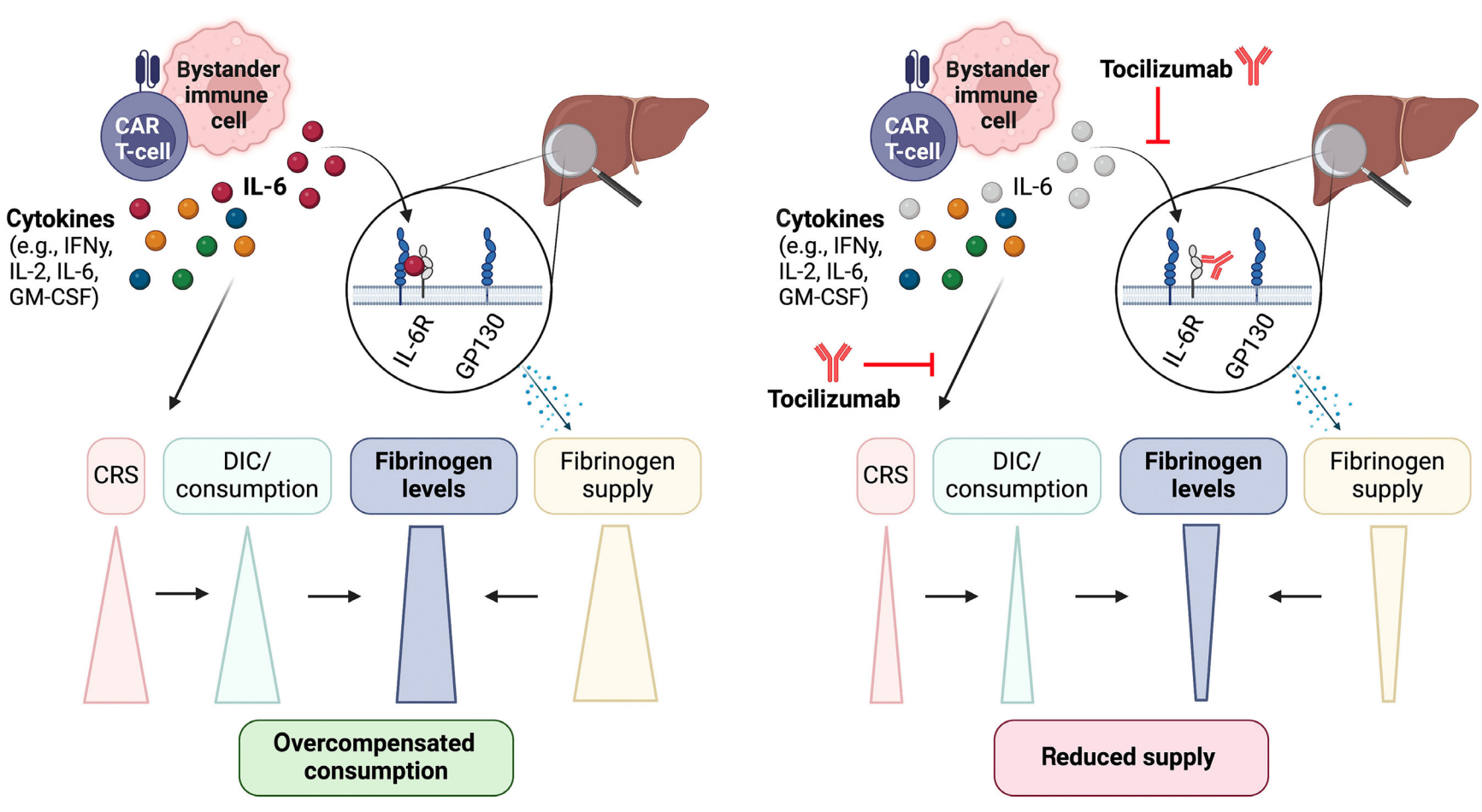

Figure 4. Proposed pathophysiology of tocilizumab-induced hypofibrinogenemia in cytokine release syndrome patients. During cytokine release syndrome (CRS), inflammation mediated by various cytokines leads to consumption of coagulation factors, which is compensated by IL-6-dependent upregulation of fibrinogen synthesis (left). When tocilizumab is used for the treatment of CRS, the IL-6 stimulus for increased fibrinogen synthesis in the liver is diminished. Therefore, consumption and production of fibrinogen are disparate, resulting in a persistent state of hypofibrinogenemia (right). The figure was created with BioRender.com. DIC: disseminated intravascular coagulation; IL-6R: interleukin-6 receptor; GP130: glycoprotein 130.

than 90% of our patients who received tocilizumab showed hypofibrinogenemia shortly after administration. Individual patient disease courses revealed rising fibrinogen levels in CRS, but rapidly declining levels after administration of tocilizumab (*Online Supplementary Figure S2*).

Logistic regression confirmed that administration of tocilizumab was the most important, independent risk factor for the development of hypofibrinogenemia. It must be noted that, due to the number of patients included, we were limited in our ability to include various parameters in the multivariate analysis (e.g., underlying malignant condition). Thus, larger prospective studies in patients treated with CAR T cells (including pediatric patients) are required. Both the duration and severity of hypofibrinogenemia showed significant correlations with the number of tocilizumab doses and the cumulative dosage, aligning with its known dose-dependent effects and half-life.[33] This observation prompts a re-evaluation of the optimal duration and dosage of tocilizumab for CRS management after CAR T-cell therapy. While current manufacturer's instructions and international guidelines recommend the administration of up to 4 doses of tocilizumab,[13] recent research suggests limiting it to 2 doses.[37]

In our patients, and in line with previous reports,[18] hypofibrinogenemia had no relevant impact on PFS for patients treated with CAR T cells (*Online Supplementary Figure S1*). Only 3 cases of bleeding and/or thrombotic events were observed, probably due to close monitoring and supplementation of coagulation factors and/or prophylactic anticoagulation.

In summary, our clinical findings suggest the following: CRS after CAR T-cell therapy drives inflammation via proinflammatory cytokines, which results in: i) activation of the coagulation system and consumption of coagulation factors including fibrinogen; and ii) increased fibrinogen synthesis through an IL-6-driven acute phase reaction (Figure 4). This excessive fibrinogen production compensates for the consumption, resulting in hyperfibrinogenemia in CRS. IL-6 receptor antagonism by tocilizumab blocks IL-6-induced fibrinogen synthesis in the liver and causes hypofibrinogenemia even in low-grade CRS. In advanced CRS stages and IEC-HS, DIC and liver dysfunction aggravate tocilizumab-induced hypofibrinogenemia.

These findings underscore the need for monitoring of fibrinogen levels in patients receiving CAR T cells treated with tocilizumab for CRS, even after discharge. Additionally, it is mandatory to continue evaluating the optimal management of CAR T-cell therapy-associated toxicities in future prospective trials, and to evaluate the effects of IL-6 receptor blockade in mechanistic studies.

Disclosures

MP received travel grants and honoraria from Kite and Takeda. HP is a consultant for Gilead, AbbVie, Pfizer, Novartis, Servier, and BMS, received research funding from BMS, and received honoraria from Novartis, Gilead, AbbVie, BMS, Servier, and Janssen-Cilag. WH received honoraria and travel grants from Amgen and Janssen-Cilag. DW received research funds from Novartis, and honoraria from Novartis, Mallinckrodt, Incyte, Sanofi, Behring, Takeda, and Gilead. MAF received honoraria from Novartis. None of the other authors have any conflicts of interest to disclose.

Contributions

MP and MAF designed the study, treated the patients, collected clinical data, performed data analysis, designed the figures and tables, and wrote the manuscript. DCH, KH and LK collected clinical data and revised the manuscript. MS, US and ME treated the patients, made the clinical observation, proposed the mechanism, and revised the manuscript. MH, SH, LH, WH, HP and DW discussed the data and revised the manuscript. CH designed the study, discussed the data, and revised the manuscript. AI-assisted technologies (DeepL, GPT-4 Turbo) were used to check the language in selected sentences.

Data-sharing statement

The data will be made available at any time upon personal request.

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