Transfusion Medicine and Hemotherapy

Research Article

Transfus Med Hemother 2023;50:218–225
DOI: 10.1159/000526786

Received: March 31, 2022
Accepted: August 24, 2022
Published online: November 29, 2022

Regulatory Measures to Improve the Safety of CAR-T-Cell Treatment

Philipp Berg Sonja Schönefeld Gabriele Ruppert-Seipp Markus B. Funk

Division Safety of Medicinal Products and Medical Devices, Paul-Ehrlich-Institut, Langen, Germany

Keywords

Chimeric antigen receptor-T-cell safety · Pharmacovigilance · Risk minimization · Cytokine release syndrome · Advanced therapy regulation

Abstract

Introduction: Regulatory activities aim to facilitate the safe use of novel therapeutics such as genetically engineered chimeric antigen receptor (CAR)-T cells. Toxicities associated with CAR-T-cell therapies have led to modified safety management guidance in clinical trials and the implementation of post-marketing requirements. The aim of this study was to estimate the effect of individual risk-minimizing measures to evaluate the appropriateness of regulatory activities. ***Methods:*** We re-examined clinical trial data prior to and after the introduction of revised treatment guidelines; we analysed spontaneous adverse drug reaction (ADR) reports submitted to the EudraVigilance database in 2019/2020 regarding their completeness; and we performed a survey of treatment centres in Germany that have been qualified for the use of commercial CAR-T cells. ***Results:*** Lower combined incidences of severe cytokine release syndrome (CRS) as well as neurotoxicity occurred following CAR-T-cell treatment after a revision of management guidelines, suggesting earlier intervention compared to before (12.6% vs. 20.5%). Numerous post-marketing ADR reports lacked information important for case assessment. Full details on treatment indication, CRS onset, outcome, and grading were available for just 38.3% of CRS cases. Survey responses support the majority of regulatory requirements for centre qualification. Time investment was highest for training of healthcare professionals, which required an average of 6.5 staff members (range 2–20) and lasted more than 2 days per person in half of the facilities. The need to harmonize the regulatory requirements for the different CAR-T-cell therapeutics was emphasized. ***Conclusion:*** Defined regulatory measures can support the safe and effective use of new therapies and are indicated for structured recording of post-marketing data, and the evaluation of such measures appears to be necessary for the continuous improvement.

Introduction

Cancer immunotherapy by means of genetically engineered T cells is a promising new therapeutic strategy but can cause serious adverse reactions. The expression of a chimeric antigen receptor (CAR) endows T lymphocytes with specificity for selected cell surface molecules. In clinical trials, CAR-T cells showed remarkable therapeutic effects in patients suffering from relapsed or refractory B-cell malignancies [1–3]. By the end of 2021, three anti-CD19 autologous CAR-T-cell products, Yescarta (axicabtagene ciloleucel [axi-cel]), Kymriah (tisagenlecleucel [tisa-cel]), and Tecartus (brexucabtagene autoleucel [brexu-cel]), received marketing authorization based on favourable clinical data from phase I/II clinical trials [4, 5]. In the EU, all three medicinal products were subjected to an accelerated assessment (PRIME designation scheme) in order to facilitate the development and clinical translation of advanced therapy medicinal products that target unmet medical needs.

Karger@karger.com
www.karger.com/tmh

Correspondence to:
Markus Funk, markus.funk@pei.de

CAR-T cells are associated with a range of toxicities that can be life-threatening, including neurotoxicity (NT) and cytokine release syndrome (CRS). The systemic inflammatory response CRS, for example, can cause widespread organ dysfunction. In some clinical trials, more than 90% of all patients presented with at least a mild form of CRS necessitating close monitoring. More severe CRS requiring intensive care (grade 3 and higher) occurred in up to 22% of DLBCL patients [6–8] and in up to 46% of ALL patients [9]. The IL-6 receptor antagonist tocilizumab is used alone or in combination with corticosteroids to manage and reverse life-threatening manifestations of CRS [10, 11] and other treatment options are investigated [12]. The clinical presentation of NT can vary but may lead to life-threatening conditions including cerebral oedema and may require corticosteroid therapy [10–13]. The occurrence of NT was reported for 40% of B-ALL patients (including 13% grade 3) [9] and some form of NT occurred in 63% (31% grade 3 and 4) of MCL patients [14].

In view of the short-term toxicities associated with the treatment, early detection and prompt management are critical to mitigate adverse outcomes and to maximize the chance for a therapeutic benefit. This is relevant for clinical development as unexpected adverse reactions can cause trials to be suspended or terminated [13, 15] and for the time after marketing approval. For the post-marketing setting, additional risk mitigation activities were imposed for all three CAR-T-cell products in the EU (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526786). The requirements consist of an educational programme to provide adequate training to healthcare professionals and a controlled distribution programme to ensure appropriate qualification and preparation of treatment centres.

A key question in the translation and regulation of new therapies is how regulatory activities can facilitate their safe use with the aim to make new treatment options available to patients while ensuring proper risk management and continued data collection. To evaluate and adjust regulatory tools during the medicine life cycle, a robust database is necessary. In order to review and evaluate the appropriateness of regulatory activities, we investigated the effect of individual risk minimizing measures based on pharmacovigilance data and the quality of post-marketing adverse reaction reports and performed an exploratory survey of treatment centres qualified for CAR-T-cell therapy.

Material and Methods

Clinical Trial Data

To estimate the impact of an investigator's brochure (IB) amendment concerning treatment recommendations in subjects with CRS or NT, Kite/Gilead – the marketing authorization holder for Yescarta (axicabtagene ciloleucel) – provided selected data of eight clinical trials (EudraCT 2015-005007-86, 2015-005008-27, 2017-001912-13, 2017-002261-22, 2019-002291-13, and ClinicalTrials.gov NCT02926833, NCT03153462, NCT03704298), including a total of 577 subjects for this regulatory evaluation.

From June 08, 2017, a new IB version introduced a recommendation to start tocilizumab treatment earlier in the case of CRS, i.e., already from CRS grade 2 or CRS grade 1 if persistent for >72 h. Previously, tocilizumab was limited to CRS grade 3 and higher, or in CRS grade 2 if subjects were elderly or suffered from concomitant comorbidities. For the treatment of neurological events, tocilizumab was no longer recommended with the exception of a concurrent CRS instead of the previous treatment algorithm (NT grade 3 and above). In addition, consideration of earlier prophylactic treatment with anti-epileptics from NT grade 1 instead of grade 2 and starting corticosteroids from grade 2 instead of grade 3 was advised (online suppl. Table 2). Thus, this point in time was chosen as reference date for comparison of safety data of subjects treated before (156 subjects) and after the IB amendment (421 subjects), respectively.

Subjects suffering from serious CRS and/or NT (n = 85) were divided into one of the following groups:

- Group 1: CRS ≥ grade 3 without NT ≥ grade 3 ("severe CRS")
- Group 2: CRS ≥ grade 3 with NT ≥ grade 3 ("severe CRS and NT")
- Group 3: NT ≥ grade 3 without CRS ≥ grade 2 ("severe NT")

The company provided the following information on individual subjects with serious CRS or NT: maximum grade of reaction, time to onset, duration, and outcome for CRS/NT, respectively. The scale from Lee et al. 2014 [16] was used for grading CRS and NT according to CTCAE 4.03. The frequency of severe CRS ≥ grade 3 and/or NT ≥ grade 3 and time to onset (median/range, mean/standard deviation) of CRS and NT were calculated for groups 1 to 3 before and since June 08, 2017.

Since data collection was not specifically designed for the regulatory aspects of this evaluation, we focused primarily on a descriptive statistical evaluation. For comparison of relative CRS/NT frequencies, relative risks, their confidence intervals (CIs), and Fisher's exact test were calculated using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA).

Analysis of Spontaneous Adverse Reaction Reports

To extract information provided to EudraVigilance [17], we searched the database for reports with the products Yescarta (axicabtagene ciloleucel), Kymriah (tisagenlecleucel), and Tecartus (brexucabtagene autoleucel). Only spontaneous (i.e., unsolicited) post-marketing reports from the European Economic Area and Switzerland submitted between January 01, 2019 and December 31, 2020 were included. Reports were screened for duplicates based on source country, patient age and sex, as well as treatment, and adverse reaction details. Reports were analysed for the following information: country of origin; seriousness; indication; CRS (including cytokine storm); NT (including the terms NT, immune effector cell-associated NT syndrome, encephalopathy, CAR-T-cell-related encephalopathy syndrome; in case of indicative terms such as "metabolic encephalopathy" and "confusional state" the free-text narrative was consulted to evaluate if reported as CAR-T-cell-related NT). For all reports describing CRS, we further analysed available data, including the narrative, on reaction onset, grading, and outcome as well as the cause of death, if applicable.

Significance of a Controlled Distribution Programme (Qualified Clinical Setting)

In order to evaluate the training measures provided by the pharmaceutical manufacturers as well as the required qualification of the apheresis facilities, healthcare professionals (HCPs) at qual-

Table 1. Subject population in axicabtagene ciloleucel (Yescarta) clinical trials evaluated regarding updated treatment recommendations

Time of treatment	Total subject population in clinical trials		Subjects with severe CRS/NT (group 1–3*§#)	
	numbers, *n*	percentage [%]	numbers, *n*	percentage [%]
Before IB amendment	156	27.04	32	20.51
Since IB amendment	421	72.96	53	12.59
Total	577	100	85	14.73

* Group 1: CRS ≥ grade 3 without NT ≥ grade 3 ("severe CRS"). § Group 2: CRS ≥ grade 3 with NT ≥ grade 3 ("severe CRS + NT"). # Group 3: NT ≥ grade 3 without CRS ≥ grade 2 ("severe NT").

ified centres were asked to answer a standardized questionnaire in 2020. After telephone contact, the questionnaire (online suppl. material) was sent to a total of 10 centres with experience in CAR-T-cell therapy in Germany, 5 centres for paediatric, and 5 centres for adult patients.

A survey was conducted at the apheresis centres on the following issues:

- the necessity and time of accreditation according to the EU Directive 2002/98, as well as registration with the International Council for Commonality in Blood Banking Automation (ICCBBA);
- the necessity and timing of an establishment according to the EU guideline for good manufacturing processes;
- the need, the problems, and the time required to train the medical staff with regard to the ordering process and labelling of the leukapheresis material;
- the need, the problems, and the time required to train the medical staff with regard to the collection, processing, cryopreservation, and shipping of the leukapheresis material.

Therapy centres were asked about:

- the need, the problems, and the time required to train medical staff on the HCP educational programme;
- the need and timing of establishing a treatment centre and the hospital pharmacy including an implementation of a (communication) procedure between the treatment centre and the hospital pharmacy.

The surveyed centres were able to make suggestions for improving the regulatory requirements in a free-text field.

Results

Effect of Revised Treatment Recommendations

To estimate the effectiveness of risk minimization by optimizing management guidance, we compared the share of subjects experiencing severe CRS and/or NT in clinical trials with Yescarta prior to and after an IB modification, recommending refined management guidelines for CRS and NT, which included an earlier start of tocilizumab treatment for CRS and corticosteroid administration for NT.

Serious CRS and NT occurred in 85 of all 577 subjects treated (14.7%, Table 1) assigned to three groups according to the symptoms observed. The three groups included (1) severe CRS, (2) severe CRS and NT, and (3) severe NT.

The overall percentage of patients reporting CRS and/or NT was higher in subjects treated before the IB amendment than in subjects treated thereafter (20.5% vs. 12.6%, $p = 0.0239$ by Fisher's exact test, relative risk 1.494; 95% CI 1.077–2.008). There was also a numerical trend evident for the three groups independently (Table 2) with 5.13% versus 2.38% for severe CRS (relative risk 1.679; 95% CI 0.947–2.583), 5.77% versus 4.28% for severe CRS and NT (relative risk 1.247; 95% CI 0.6874–2.004), and 9.62% versus 5.94% for severe NT (relative risk 1.428; 95% CI 0.9038–2.085) although not reaching statistical significance. A tendency to a higher time to onset was observed in the severe CRS dataset after IB amendment (median [range] in days: 3 [0–17] vs. 1 [0–4]), while time to onset was similar in the severe CRS and NT and the NT groups.

Evaluation of the Information Content of Spontaneous Adverse Reaction Reports

To investigate the data accuracy of spontaneous ADR reports, we extracted information from the European pharmacovigilance database EudraVigilance. Listings of 811 reports were retrieved, including 29 cases of report duplications. A total of 782 spontaneous individual case safety reports (ICSRs) related to commercial CAR-T-cell therapies and submitted to the EudraVigilance database in 2019 and 2020 were identified and further analysed. The reports originated from 19 countries, of which four countries accounted for 84.7% of all reports (France 25.6%, UK 22.3%, Germany 19.7%, and Spain 17.1%). With over 10 ICSRs each, Italy, Switzerland, Netherlands, and Austria accounted for 11.0% of reports. With less than 10 ICSRs each, Czech Republic, Portugal, Croatia, Ireland, Poland, Belgium, Greece, Sweden, Norway, Denmark, and Slovenia accounted for the remaining 4.3% of the reports.

The majority of reports were classified as serious (93.5%), and in 15.6%, a fatal outcome was reported (Table 3). CRS was reported to have occurred in 494 cases (63.2%) and NT in 268 cases (34.3%). In 52 reports (6.6%),

Table 2. Impact of amended treatment recommendations on serious CRS[a] and NT[b] incidence following treatment with axicabtagene ciloleucel

Temporal relationship to IB amendment	Group 1 "Severe CRS"		Group 2 "Severe CRS + NT"		Group 3 "Severe NT"	
	before	since	before	since	before	since
Percentage of all subjects (%)	5.13	2.38	5.77	4.28	9.62	5.94
Number of subjects	8	10	9	18	15	25
Time to onset of CRS, days						
Median	1	3	1	1		
Range	0–4	0–17	0–5	0–6		
Mean	1.50	4.60	1.44	1.61		
Standard deviation	1.60	5.17	1.51	1.33		
Time to onset of NT, days						
Median			5.00	4.50	5.00	5.00
Range		1–6	1–13	1–16	0–18	
Mean		4.00	4.72	4.93	5.96	
Standard deviation		1.94	3.04	3.51	3.81	

Group 1: CRS ≥ grade 3 without NT ≥ grade 3, group 2: CRS ≥ grade 3 with NT ≥ grade 3, group 3: NT ≥ grade 3 without CRS ≥ grade 2.
[a] Modified Lee et al. 2014 [16]. [b] Grading assessment CTCAE 4.03.

NT occurred without CRS, while in 216 ICSRs NT was described for patients for whom CRS was reported as well (i.e., 27.6% of all reports; 80.6% of NT reports). Haemophagocytic lymphohistiocytosis or macrophage activation syndrome, in addition to CRS, was reported in 15 cases (3% of CRS reports).

Grading for CRS severity was provided by the reporter in 57.5% of ICSRs and, among those, CRS grade 3 and 4 occurred in 21.8% of patients (Table 3). A CRS grade 5, i.e., as death due to CRS as the main factor, was explicitly reported in two cases. Nevertheless, CRS occurred in 68 cases out of 122 with a fatal outcome (i.e., 55.7%); in 26 instances, CRS could represent a possible co-factor for death, and no cause for death was specified in 19 cases. Of all spontaneous ICSRs reporting CRS, a treatment indication was provided in 80.6%, onset of CRS in 73.7%, an outcome in 75.7%, and a severity grading in 57.5%. Information on all variables – treatment indication, CRS onset, outcome, and grading – was present in just 38.3% of reports. Collective reports providing pooled information on several patients, without individual details, such as indication or date of treatment, contributed to the share of incomplete reports. While some case reports provided extensive details on the patient's medical history, the adverse reactions, including their diagnosis and management, other reports contained little clinical information and were considered as not assessable and not appropriate to characterize the product's safety profile any further.

Evaluation of Requirements to Qualify Treatment Centres

To evaluate the implementation effort and usefulness of additional risk minimization measures associated with

Table 3. Characterization of spontaneous adverse reaction reports related to approved CAR-T-cell treatments submitted to EudraVigilance in 2019 and 2020

Safety report characteristics	*N*	%
Total reports	782	100
Classified as "serious"	731	93.5
Fatal outcome	122	15.6
CRS	494	63.2
NT	268	34.3
Characteristics of CRS reports	*N*	%
Reports with CRS	494	100
CRS as only ADR reported	164	33.2
CRS and NT	216	43.7
CRS and other ADRs (excluding NT)	114	23.1
CRS grading		
CRS grade 1	100	20.2
CRS grade 2	120	24.3
CRS grade 3	45	9.1
CRS grade 4	17	3.4
CRS grade 5	2	0.4
CRS grade not provided	210	42.5
Total cases with fatal outcome	122	100
CRS occurred	68	55.7
CRS possible co-factor for death	26	21.3
Cause of death not reported	19	15.6
Completeness of CRS reports	*N*	%
Reports with CRS	494	100
Indication provided	398	80.6
Onset of CRS provided	364	73.7
Outcome of CRS provided	374	75.7
CRS grading provided	284	57.5
Indication, CRS onset, outcome, and grading provided	189	38.3

CRS, cytokine release syndrome; NT, neurotoxicity.

Table 4. Survey of 8 treatment centres – implementation of regulatory requirements

Regulatory requirements	Meaningful requirement?	Workable requirement?	Established before CAR-T-cell therapy?	Implementation		Time spent on implementation
Quality audit	Yes	Yes	Yes	No difficulties	Difficulties	Days
Apheresis centre: accreditations/licenses according to directive, ICCBBA registration	4/8	4/8	3/8	6/8	2/8	1 centre: >2 2 centres: 1–2
Implementation of guidelines for GMP	6/8	6/8	7/8	7/7	0/7	1 centre: >2 4 centres: 1–2 1 centre: <1
Therapy centre: establishment of a procedure (communication) between the treatment centre and the hospital pharmacy	8/8	8/8	5/8	8/8	0/8	2 centres: 1–2 5 centres: <1
	Meaningful requirement?	Workable requirement?	How many employees trained?	Implementation		Time spent on implementation
Training	Yes	Yes	Number	No difficulties	Not helpful	Days per person
Training the HCP educational programme	7/8	8/8	2–20 mean: 6.5	3/8	5/8	4 centres: >2 3 centres: 1–2 1 centre: < 1
Training the ordering process, including proof of identity	7/8	8/8	2–8 mean: 4.3	8/8	0/8	6 centres: 1–2 1 centre: <1
Training the leukapheresis reference manual	6/8	7/8	4–6 mean: 4.7	7/7	0/7	1 centre: >2 5 centres: 1–2 1 centre: <1

GMP, good manufacturing practice; ICCBBA, International Council for Commonality in Blood Banking Automation; HCP, healthcare professional. As not every centre answered all questions, complete results cannot be presented for all questions.

approved CAR-T-cell products, we developed a standardized questionnaire for treatment centres. Eight of the ten centres surveyed provided information on most questions, 4 treatment facilities for paediatric patients and 4 for adult patients. A total of 94 patients had undergone CAR-T-cell treatment in the institutions that provided feedback by autumn 2020; of them, 55 paediatric patients and 39 adults, an average of 12 patients (median: 10, range: 2–33) per centre. JACIE accreditation was established at seven centres, before participation in treatment with CAR-T cells. At seven centres, the clinic and apheresis unit were separated areas with different personnel responsibilities. Answers of the questionnaires are shown in Table 4.

Two apheresis-facility performing cell separation in paediatric patients stated that the accreditation according to the directive 2002/98 and ICCBBA registration was difficult. The reason given was the specifics of the preparation and performing of apheresis in small children.

Seven of the eight treatment facilities stated that training for the HCP educational programme is a meaningful and practical requirement, but current implementation was not helpful. In particular, the limited expertise of some trainers was criticized. However, GMP guidelines and other requirements were classified as sensible and feasible by the treatment facilities.

An average of 5–6 people per centre took part in each of the training measures; in larger facilities even more medical staff members were involved. For most of the requirements, the training lasted 1–2 days per participant, especially, for the HCP educational programme, four facilities required more than 2 days per person.

The following suggestions were made to improve or facilitate the regulatory procedure:

- Joint cross-product qualification was required as desirable and necessary. Company-specific requirements for each of the CAR-T-cell preparations seem not useful. Physicians stated that implementation of product-specific requirements for the use of several CAR-T-cell preparations would not be feasible.
- Streamlining and improving company-provided training is required. However, training was classified a useful preparation and enabled a review of internal communication and standards.

- A product-independent introduction of online documentation for the apheresis units was considered helpful.
- Additional demands by national supervisory bodies were considered not necessary and sometimes counterproductive (e.g., provision of additional medical care).

Discussion

Effect of Revised Treatment Recommendations

Safety standards of novel therapeutic modalities are continuously improved. Our comparison of Yescarta clinical trial data prior to and after an IB amendment shows a trend towards lower numbers of serious CRS and NT cases after the introduction of revised treatment recommendations. This is in agreement with growing clinical evidence that early intervention with tocilizumab can reduce the frequency of severe CRS without attenuating the CAR-T cells' therapeutic effect [18, 19] and, in the meantime, has been incorporated in respective guidelines [20–23]. In addition to improvements in diagnosis and management standards, new concepts are investigated to produce effective CAR-T cells with reduced toxicities [24].

A limitation of our retrospective evaluation is based on pooled data from different clinical trials for NHL, with different indications and differences in study protocols. In addition, these data were not specifically collected and documented for a regulatory evaluation. Moreover, clinical experience and management standards are evolving fast in this field, as reflected in the revised treatment guidelines. Despite these limitations, our data show the need for regulatory requirements to reduce serious adverse reactions of CAR-T-cell therapy.

Evaluation of Spontaneous Reporting Suggests Need for Structured Recording of Adverse Reactions.

Reporting of suspected ADRs after marketing approval forms the foundation of any pharmacovigilance system. We demonstrated that the European pharmacovigilance database EudraVigilance contains already over 700 ADR reports related to recently approved CAR-T-cell products. Based on the analysis performed, this data set reveals no new or unexpected safety information. However, it highlights considerable variability in the quality and completeness of ADR reports. A significant fraction of reports lacks important details such as treatment indication, time to adverse reactions, severity, management, and outcome of ADRs as well as cause of death in the case of fatal outcome. Of all reports in which CRS occurred, details on the complete set of variables treatment indication, CRS onset, outcome, and grading were presented in just over a third (38.3%). Incomplete data is a known limitation of drug safety surveillance based on spontaneous ADR reporting after marketing authorization [25, 26] and our evaluation indicates this is also true for CAR-T-cell products.

Patients treated in the post-marketing setting show greater variability than in clinical trials, which possibly influences clinical outcomes and is the reason for interest in post-marketing data. While initial real-world reports largely confirm clinical trial data [27–31], others question previously reported response rates [32]. Of note, with few exceptions [33], these real-world reports originate mostly from the US centres that were already involved in the products' clinical development. As confirmation of pre-approval clinical trial data is sought in the real-world setting, to rule out centre effects and due to limitations of spontaneous pharmacovigilance data, as highlighted in our analysis, there is a need for a structured recording of adverse reactions, for example, by means of patient registries [34]. In order to enable adequate case assessment, a precise collection of meaningful data is essential.

Evaluation of Requirements for a Qualified Clinic

Although only a limited number of the treatment centres took part in the survey, there are some important suggestions regarding the introduction of regulatory measures to improve safety standards. It turned out that most of the required criteria have already been established in treatment centres in Germany. Nevertheless, requirements must be adapted to the national situations. The JACIE accreditation, which has already been carried out at the majority of the treatment centres, seemed to represent a good basis for a quick and qualified implementation of the required regulations.

Most regulatory requirements for centre qualification were rated as meaningful and workable by the institutions surveyed. An accreditation according to the Directive 2002/98 and the registration with the ICCBBA had not been established in the majority of the institutions and were viewed critically. Half of the physicians surveyed rated these requirements as unnecessary or not workable. Two centres reported difficulties in implementation and stated that cell separation in paediatric patients requires an individual and specific approach that can be described only to a limited extent in a guideline.

In addition, the time and personnel requirement for training was rated as unexpectedly high, which should be taken into account before CAR-T-cell therapy is established. It was also proposed that the training course should be well prepared and carried out by qualified experts. In addition, respondents recommended a standardized training programme and, if necessary, the development of clear guidelines for the implementation of the educational programme. Some interviewees also suggest-

ed the participation of treatment facilities in the development of the trainees' programmes. As the use of CAR-T-cell therapies poses new challenges and requirements for all parties involved, cooperation in improving regulatory measures would be a new but a conceivable approach.

The proposed establishment of product-independent documentation for the implementation of the apheresis procedure seems sensible, but this would require cooperation between various pharmaceutical companies, which has not yet taken place. Since data are limited regarding the benefit of the required treatment centres qualification and additional risk minimization measures in general [35, 36], a review of the usefulness and appropriateness of defined regulatory measures appears necessary in any case and should be carried out through systematic surveys of the treating physicians.

Outlook

The pre-clinical and clinical development of CAR-T-cell therapies has expanded rapidly in recent years and includes a growing range of targets and tumour types [37]. A variety of clinical trials is ongoing with already commercially available CAR-T-cell therapies [38] and progress in clinical trials occurs at the same time as the new medicines have become available to patients and valuable post-marketing experience accumulates in real-world settings. Together, this knowledge contributes to the development of best practice recommendations in the clinic and patient care [20–22], improved management of adverse reactions [12, 23], and continuous safety monitoring, which should help to reduce heterogeneity in clinical practice between centres [39] and improve the benefit of these new therapies – both in clinical trials and post-marketing.

In conclusion, our findings indicate that defined regulatory measures can support the safe and effective use of new advanced therapies, and the evaluation of such measures, in particular post-marketing requirements, appears necessary for the continuous improvement and adaptation in light of the developing on-site conditions, needs, and standards.

Acknowledgments

We thank colleagues at the Paul-Ehrlich-Institut for assistance in data acquisition and for fruitful discussions and all treatment centres who provided feedback on regulatory requirements.

Statement of Ethics

Not applicable. No clinical trials were performed as part of this study. PEI as the national competent authority is responsible for the safety of CAR-T-cell products in Germany.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Funding Sources

No external funding was received for this study.

Author Contributions

Philipp Berg, Gabriele Ruppert-Seipp, and Markus Funk developed the concept. Sonja Schönefeld and Gabriele Ruppert-Seipp collected and analysed clinical trial data. Philipp Berg collected and analysed spontaneous adverse reaction reports; Markus Funk developed a standardized questionnaire and analysed data of qualify treatment centres. Philipp Berg, Sonja Schönefeld, Gabriele Ruppert-Seipp, and Markus Funk wrote the manuscript, have critically revised and approved the final version of the manuscript, and fulfil the ICMJE criteria for authorship.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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