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Systematic Review

The Magic of the Immunotherapy CD-19 CART Therapy in Treatment of Patients with Variable Haematological Malignancies, and One of its Draw Back as Hypogammaglobulinemia: Systemic Review with Meta-Analysis

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Abstract

Aim: To determine the effect of CART therapy on hypogammaglobulinemia, and to determine the probable medications in management of hypogammaglobulinemia and associated risk factors and complications.

Methodology: Systematic search was conducted in 4 databases using the terms CART therapy, haematological malignancies, and hypogammaglobulinemia. Articles including patients with any haematological malignancies undergone CART therapy and assessment done on hypogammaglobulinemia were included. Following screening and selection of the articles, narrative synthesis, quality assessment, and meta-analysis were conducted.

Result: From the 4 databases 1197 citations were retrieved of which 9 were finally included for narrative synthesis and meta-analysis comprising of 425 patients who were affected due to any haematological malignancies and had undergone CART therapy. The overall incidence rate was 35.35%. In all the studies, hypogammaglobulinemia was managed using IgG. Most of the patients across the studies had infection due to reduction in WBC count. The overall incidence of neutropenia following CART therapy was 59%, lymphopenia was 82%, and B-cell aplasia was 49.5%.

Conclusion: The effective way for management of hypogammaglobulinemia was using IgA antibody. The overall incidence of hypogammaglobulinemia and WBCs was difficult to conclude as majority of the studies were of low and fair quality and were collected at different time points after administration of CART therapy. Thus, good quality clinical trials, open label trials or RCT are required. Hypogammaglobulinemia increases with a decrease in neutrophils, lymphocytes, and B-type cells. Thus, the number of infective patients increases initially and slowly decreases.

Keywords: *Acute Lymphocytic Leukaemia (ALL); Chronic Lymphocytic Leukaemia (CLL); Acute Myeloid Leukaemia (AML); Chronic Myeloid Leukaemia (CML); Non-Hodgkin's (NHL); Chimeric Antigen Receptor T-Cell Therapy (CART Therapy)*

Introduction

Haematological malignancies have emerged as a leading cause of disability and mortality globally. Haematological malignancies are related to the blood, bone marrow, and lymph nodes. These include different types of leukaemia (acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML)), myeloma, and lymphoma (Hodgkin's and non-Hodgkin's (NHL)). Cumulatively, these hematologic malignancies account for 9% of all diagnosed, incident cases of cancers in the United States in the year 2017. Epidemiologically, lymphomas are more common than the leukaemia or myeloma [1].

One of the primitive forms of immunotherapy is allogeneic hematopoietic stem cell transplantation (HCT). In 1968 E. Donnall Thomas performed the first allogenic transplant. He won the Nobel Prize for being a pioneer in the field [2]. Immunotherapies utilize different ways to attack tumour/malignant cells. Immunotherapies can be categorised into three groups: Checkpoint inhibitors, Cytokines, and Cancer vaccines. Also, immunotherapies may be used alone or in combination with other treatments such as surgery, chemotherapy, radiation therapy, and targeted therapy. When compared to other modalities of treatment, for example, surgery, chemotherapy and radiotherapy, immunotherapies are comprehensive and less cytotoxic. This is because this type of therapy utilizes the power of the immune system to attack the cancer cells and no synthetic chemicals are introduced into the body.

Chimeric antigen receptor T-cell therapy (CART) is a type of immunotherapy where patients T-cells are first extracted, genes for CAR receptors are then added to the cells *in-vivo*, such cells are then replicated in large numbers in the laboratory and introduced into the patient's body to fight malignant cells [3]. These modified T-cells can bind to antigens on the malignant cells and kill them. CART therapy is also popularly known as adoptive cell therapy, adoptive immunotherapy, or immune cell therapy. Immunotherapy for hematologic malignancies has gained popularity in recent years and among them, CART therapy is the most popular one, especially due to the high response rate among children has led to its wide usage [4]. Past research has been promising where terminal patients have shown full recovery of up to 92% in acute lymphocytic leukemia [5]. CART therapies have been developed and modified through the years and investigated in several clinical studies. CARs with target-specific scFv fused to the CD3ζ end domain of the TCR/CD3 complex were first generated. This showed drawbacks, for example, less persistence, expansion, and antitumor efficacy during laboratory research. Hence, a newer second-generation CAR was created that incorporated cytoplasmic signalling domains of T-cell costimulatory receptors. Following this, third-generation CAR was developed with multiple costimulatory domains [6]. CD19 CAR-T therapy is a newer generation therapy targeting CD19 cells.

Even after possessing the significant anti-lymphoma activity, this CART cell therapy has unique toxicities like B-cell aplasia, hypogammaglobulinemia, cytokine release syndrome (CRS), acute neurotoxicity, and other infectious complications. Till date, there is a limited data on the infectious risks related to post CART cell therapy [7,8]. Hypogammaglobulinemia (HG) is associated with recurrent and severe infections and malignancies, for example, chronic lymphocytic leukaemia (CLL), non-Hodgkin lymphoma (NHL), multiple myeloma, and Waldenström Macroglobulinemia (WM). It is characterized by a decrease in total serum immunoglobulin (Ig) levels leading to immunodeficiencies [9].

Being a novel treatment method, clinical trials related to the effects of CD19 CART therapy have been conducted but are presently inconclusive. This systematic review will help bridging the gap and bring conclusion by compiling different studies as previously no such systematic review has been conducted. This systematic review will help in understanding the incidence of hypogammaglobulinemia, toxicity associated with CART therapy, management of hypogammaglobulinemia, and associated risk factors related to the incidence of infection following CART therapy.

Methods

Searching

Systematic search was conducted in 4 databases PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Clinicaltrials.eu, and Clinicaltrials.gov databases using the search terms 'CART therapy', 'Chimeric antigen receptor Therapy', 'haematological malignancies', 'acute lymphocytic leukaemia', 'chronic lymphocytic leukaemia', 'acute myeloid leukaemia', 'chronic myeloid leukaemia', 'Non-Hodgkin's lymphoma', 'myeloma', 'Hodgkin's lymphoma', 'leukaemia', 'lymphoma' and 'hypogammaglobulinemia'. Search terms were combined using the Boolean operators and were restricted to English language and published after year 2000. Back referencing was not conducted as no such systematic review or meta-analysis was published before.

Selection and screening

Selection of the articles were conducted on two stage screening. In the first stage title and abstracts were screened and in the second stage free full text articles were screened. The inclusion and exclusion were based on PICO format. As stated below:

- Population: Patients with any haematological malignancies such as acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, myeloma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma.
- Intervention: CART cell therapy.
- Comparator: Placebo or immune therapy.
- Outcome: Incidence of hypogammaglobulinemia, management of hypogammaglobulinemia, associated risk with hypogammaglobulinemia.
- Studies: Clinical trials, randomized clinical trials, prospective study, retrospective study.
- Year: Publication after year 2000.

Data extraction and quality assessment

Data extraction and quality assessment was done based on the study type. Data was extracted for the sample size, population type, type of intervention, previous and subsequent therapy used, incidence of infection, incidence of hypogammaglobulinemia, medication or therapy used to control hypogammaglobulinemia, associated toxicity due to hypogammaglobulinemia, and associated risk factors due to hypogammaglobulinemia following CART therapy. For quality assessment NIH quality assessment questionnaire was used [10]. Quality assessment tool for observational cohort and cross-sectional studies and Quality assessment tool for before-after (pre-post) studies with no control group were used. Based on the tool used across each study, the overall studies were marked as low, fair, or good quality studies.

Narrative synthesis and meta-analysis

Based on the type of data, narrative synthesis and meta-analysis was performed. Narrative synthesis was performed based on similarity and dissimilarity of the type of interventions, and study type. Meta-analysis was conducted based on the fixed effect model due to variation in diagnostic criteria and timeline of measuring the outcome. Heterogeneity among the studies was checked using the degree of heterogeneity (I^2 statistics) and forest plot. I^2 more than 75% was considered as high heterogeneity and less than 25% was considered as low heterogeneity. Meta-analysis was performed in Openmetaanalyst software. Pooled proportion in incidence of hypogammaglobulinemia was calculated and represented in the forest plot.

Results

The complete systematic review was conducted according to the PRISMA guidelines. Comprehensive search was conducted in PUBMED, Cochrane, Clinical trials sites of which total 1197 citations were retrieved. After conducting title, abstract and full text screening 9 articles were finally included for narrative synthesis and meta-analysis. Overall, 528 patients were included who had any sort of haematological malignancies and were treated with CART therapy as shown in figure 1 and table 1.

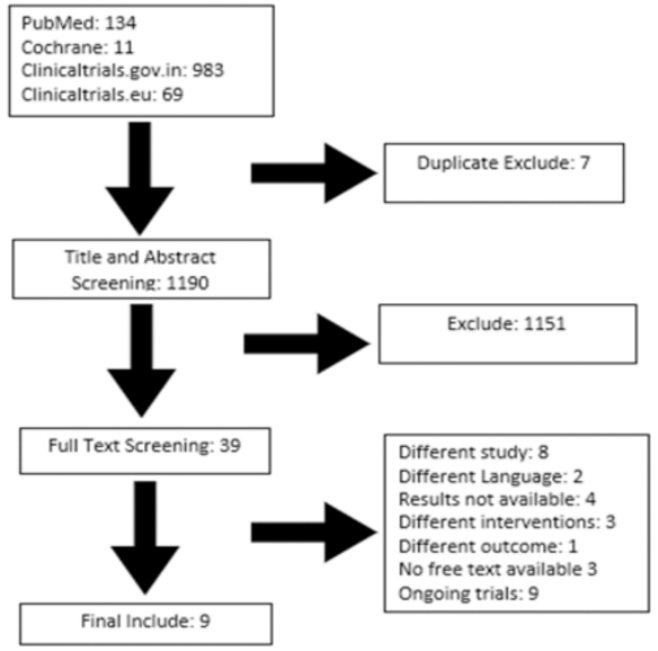

Figure 1: *PRISMA diagram for selection of studies.*

Study characteristics

There were a lot of homogeneity among the study characteristic in terms of study type, disease type, intervention, and median age. Majority of the studies were conducted in USA (Vora_2020, Wudhikarm_2020, Cordeiro_2021, Kambhampti_2021, Hill_2017), followed by UK (Roddi_2021), China (Wang_2020) and Canada (Kochenderfer_2012). In terms of study type, 5 studies (Vora_2020, Wang_2020, Cordeiro_2021, Kambhampti_2021, Hill_2017) were retrospective, 2 studies (Cappell_2020, Kochenderfer_2012) were clinical trial, one study each were open label study (Roddi_2021) and one study were prospective study (Wudhikarm_2020). All 528 patients had haematological disorder such as B-cell acute lymphoblastic leukaemia, B cell lymphoma, mixed leukaemia, multiple myeloma, B-cell lymphoma follicular lymphoma, splenic marginal zone lymphoma, Non-Hodgkin's Lymphoma, chronic lymphocytic leukaemia. In majority of the studies, the CART therapy used were CD19 (Roddi_2021, Vora_2020, Wudhikarm_2020, Cordeiro_2021, Hill_2017, Kochenderfer_2012), and rest CART therapy used were anti-CD19 (Cappell_2020), BCMA (Kambhampti_2021) and anti BCMA therapy (Wang_2020). In all the studies, the median age was above 18 years, while in one study (Vora_2020) the median age was below 18 years. Out of the 9 studies, in 8 studies the follow up ranged from median 1.5 months to 40 months. While in one study, the follow up timing for all the patients were unclearly stated (Kochenderfer_2012).

Study	Country	Study Type	Disease	Sample Size	Intervention	Follow up	Mean Age	Study Quality
Roddi_2021 [11]	UK	Non-randomized open label trial	B-cell Acute Lymphoblastic leukaemia	20	CD19-CART therapy	Median: 21.7 months	Median: 41.5 (18 to 62) years	Good
Vora_2020 [4]	USA	Retrospective study	B-cell Acute Lymphoblastic leukaemia, mixed leukaemia, and B-cell lymphoma	83	CD19-CART therapy	Median: 1.5 (0.75 to 3) months	Median: 12 (1 to 25) years	Fair
Wang_2020 [12]	China	Retrospective study	Recurrent/relapsed multiple myeloma	40	Anti-BCMA CART therapy	Mean: 16 months	Median: 55 (27 to 70) years	Fair
Wudhikarm_2020 [7]	USA	Prospective study	Diffuse large B cell lymphoma	60	CD19-CART therapy	Median: 6 (0.8 to 12) months	Median: 63 (19.5 to 85.9) years	Fair
Cordeiro_2021 [8]	USA	Retrospective study	Relapsed/refractory All, NHL, CLL	86	CD19-CART therapy	Median: 28.1 (12.5 to 62.6) months	Median: 57 (23 to 75) years	Poor
Cappell_2020 [13]		Single arm clinical trial	B-cell Acute Lymphoblastic leukaemia or primary mediastinal B-cell lymphoma, low-grade B-cell lymphoma, or chronic lymphocytic leukaemia	43	Anti-CD19 CART therapy	Median: 42 (1 to 123) months	Median: 54 (26 to 86) years	Good
Kambhampti_2021 [14]	USA	Retrospective study	Multiple myeloma	55	BCMA CART therapy	12 months	Median: 62 (33 to 77) years	Fair

Hill_2017 [15]	USA	Retrospective study	Recurrent/ relapsed Acute Lymphoblastic leukaemia, Non-Hodgkin's Lymphoma, chronic lymphocytic leukaemia	133	CD-19 CART therapy	Median: 40 (20 to 73) months	Median:54 (20 to 73) years	Fair
Kochenderfer_2012 [16]	Canada	Clinical trial	Follicular lymphoma, splenic marginal zone lymphoma or chronic lymphocytic leukaemia	8	CD-19 CART therapy	Unclear	Median: 54 (47 to 63) years	Poor

Table 1: *Study characteristics and study quality.*

Study quality

Depending on the study methodology quality assessment tool for observational cohort and cross-sectional studies and quality assessment tool for before-after (pre-post) studies with no control group were used as shown in table 1. Quality assessment tool for observational cohort and cross-sectional studies were used in 5 studies (Vora_2020, Wang_2020, Cordeiro_2021, Hill_2017, Kambhampti_2021); while quality assessment tool for before-after (pre-post) studies with no control group were used in 4 studies (Wudhikarm_2020, Roddi_2021, Cappell_2020, Kochenderfer_2012). Out of the 9 studies, 2 studies (Roddi_2021, Cappell_2020) were good quality and had low risk of bias, followed by 4 studies (Vora_2020, Wang_2020, Hill_2017, Kambhampti_2021) which were of fair quality and 3 studies (Cordeiro_2021, Wudhikarm_2020, Kochenderfer_2012) which were of low quality.

Study outcome

In terms of study outcome, there were a lot of heterogeneity in reporting of the incidence of hypogammaglobulinemia, previous therapy or and subsequent therapy, incidence of infection, management of hypogammaglobulinemia, and associated risk factors due to Hypogammaglobulinemia following CART therapy as shown in table 2. The most common prior and subsequent therapy used across the studies were allogenic, autologous transplantation, antibiotics, cyclosporamide, fludarabine, and immune therapy such as tocilizumab, inotuzumab, blinatumomab.

In 4 studies, the criteria for hypogammaglobulinemia were when the IgG level was less than 400 mg/dl and in one study severe hypogammaglobulinemia was considered when IgG level was 100 - 299 mg/dL, while in the remaining 4 studies no criteria were reported. The management therapy for hypogammaglobulinemia used across the studies were intravenous immunoglobulin G (IVIG).

The timeline for incidence of hypogammaglobinaemia varied across studies. Six studies reported incidence of hypogammaglobulinemia within short span (within 3 months or 90 days), one study reported incidence of more than 90 days and one study reported incidence throughout the study period. While two studies didn't report any incidence of hypogammaglobulinemia. The overall incidence within 30 days and 90 days were 281 (33.23%) and 163 (36.62%) respectively. Similarly, the incidence of infection as reported across the studies varied. The incidence of infection in first 90 days were 175 out of 477. In all the studies, the management of the hypogammaglobulinemia was controlled by administering intravenous immunoglobulin (IVIG). Significant risk associated factors for infection following CART therapy across the studies were prior HCT, lymphodepletion with cyclophosphamide plus fludarabine and IgG < 400 mg/dl, tocilizumab use, international staging system for haematological cancer, Performance status, immune effector cell neurotoxicity, systematic corticosteroid during CART therapy, infection before CART therapy, CART-t therapy, CRS grade, neurotoxicity grade, ICU admission, and bridge chemotherapy.

Following CART therapy, complications was observed in terms of WBCs and platelets. Six studies (Roddi_2021, Vora_2020, Wang_2020, Wudhikarm_2020, Kambhampti_2021, Hill_2017) reported complication of neutropenia, five studies (Roddi_2021, Wang_2020, Cappell_2020, Hill_2017, Kochenderfer_2012) reported complication of B-cell aplasia, three studies (Vora_2020, Wudhikarm_2020, Kambhampti_2021) reported complication of lymphopenia, and one study each reported complication of thrombocytopenia (Roddi_2021) and cytopenia (Cordeiro_2021). About 281 patients had neutropenia within 30 days and 19 patients had neutropenia continued after 30 days. B-cell aplasia occurred in 199 patients across the five studies, 95 patients had lymphopenia across three studies, 20 patients had thrombocytopenia and three patients had cytopenia.

Study	Previous/ Subsequent therapy	Criteria for Hypogammaglobulinemia	Incidence of Hypogammaglobulinemia	Incidence of Infection due to Hypogammaglobulinemia following CART therapy	Management of Hypogammaglobulinemia	Significant associated risk factor for infection following CART therapy	Blood cells complications following CART therapy
Roddi_2021 [11]	Prior: Inotuzumab ozogamicin, blinatumomab, allogenic-SCT Subsequent: Lymphodepletion with IV fludarabine, cyclosporamide, and tocilizumab	NR	Within median of 2 months: 15	Infection less than 30 days: 15 Infection between 30 to 90 days: 9 All grade infection: 2	Patient with severe and more than 1 infection were administered with IVIG	NR	Within 28 days: Thrombocytopenia Grade 1 to 2: 3 Grade 3: 3 Grade 4: 14 Within 28 days: Neutropenia: Grade 4: 20 B-cell aplasia: 15

Vora_2020 [4]	Prior: Allogenic HCT but no immune suppression therapy Subsequent: IgG	NR	Within 21 days: 12 Remaining hypergammaglobulinemic after IVIG administration: 10	Infection less than 28 days: 33 Infection between 29 to 90 days: 11	Patients with less than 400 mg/dl Ig were administered with IVIG	Prior HCT, Lymphodepletion with cyclophosphamide plus fludarabine and IgG < 400 mg/dl	Within 7 days: Neutropenia: 80 Day 63: Neutropenia: 5 Lymphopenia: 8
Wang_2020 [12]	Prior: Tocilizumab, allogenic SCT Subsequent: Fludarabine, Cyclophosphamide, GCSF and IgG.	IgG < 800 mg/dL, IgM < 50 mg/dL and IgA < 100 mg/dL	NR	Infection: 23	Patients with hypogammaglobulinemia were administered with IVIG.	Tocilizumab use, International staging system for haematological cancer	Within 28 days: Neutropenia:30 Within 70 days: B-cell aplasia: 40
Wudhikarm_2020 [7]	Prior: Allogenic and autologous HCT, bridging therapy, axicabetagene ciloleucel, tisagenlecleucel, antibiotic therapy Subsequent: Acyclovir, Trimethoprim/sulfamethoxazole, fluconazole, voriconazole	IgG less than 400	Within 30 days: 14 After 30 days: 12	Infection entire study period: 12	Patients received IVIG due to hypogammaglobulinemia	Performance status, immune effector cell neurotoxicity, systematic corticosteroid during CART therapy, infection before CART therapy,	Within 30 days: Neutropenia: 49 After 30 days: Neutropenia: 10 Lymphopenia: 35
Cordeiro_2021 [8]	Prior: Allogenic and autologous HCT. Subsequent: systemic therapy	IgG less than 400 mg/dl	Within 90 days: 34 After 90 days: 28 Prolonged hypogammaglobulinemia: 61	Infection entire study: 33	Patients received IVIG due to hypogammaglobulinemia and required intensive therapy	NR	Study period: Cytopenia: 3

Cappell_2020 [13]	Prior: Anti-lymphoma regimen, allogenic and autologous SCT	NR	Patients received normal level of Ig in all three: 6 End of study: IgA not recovered: 15 IgM not recovered: 8 IgG not recovered: 5	NR	Patients with Ig level between 400 - 500 mg/dl Ig were administered with IVIG	NR	Within 51 months B cell depletion: 24
Kambhampti_2021 [14]	Prior: allogenic and autologous transplant Subsequent: antibiotic, Tocilizumab	Normal: IgG > 600 mg/dL mild Mild to moderate: IgG 300-600 mg/dL Severe: IgG 100-299 mg/dL Profoundly reduced: IgG < 100 mg/dL.	Within 30 days: Mild to moderate: 10 profoundly Severe: 37 9-12 months: Mild to moderate: 6 profoundly Severe: 7	Infection: 29	Patients with less than 400mg/dl Ig were administered with IVIG	Bridging chemotherapy	First Month: Neutropenia grade 3 to 4: 54 Lymphopenia grade 3 to 4: 55 9 to 12 months: Neutropenia grade 3 to 4 months: 2 Lymphopenia grade 3 to 4: 4
Hill_2017 [15]	Prior: allogenic and autologous HCT: Subsequent: Granulocyte colony-stimulating factor, antimicrobial, levofloxacin, fluconazole, trimethoprim, sulfamethoxazole, IVIG	IgG less than 400 mg/dl	Between 15 to 30 days: 47 Between 31 to 60days: 36 Between 61 to 90 days: 61	First 28 days: 30	Patients with less than 400 mg/dl Ig were administered with IVIG	CART-t therapy, CRS grade, neurotoxicity grade, ICU admission	Within 28 days: Neutropenia: 14 B cell depletion: 116
Kochenderfer_2012 [16]	Prior: Cyclophosphamide, fludarabine	NR	Study period: 4	Unclear	Patients received IVIG due to hypogammaglobulinemia	NR	Within 6 months: B-cell depletion: 4

Table 2: *Study outcome.*

Meta-analysis

Using the inclusion and exclusion criteria, similarity was found across population and the intervention. However, dissimilarity was found for outcome data across the studies. In terms of outcome, the incidence of hypogammaglobulinemia, neutropenia, B-cell aplasia, and lymphopenia were considered at different time points. Moreover, the criteria used for measuring the hypogammaglobulinemia varied across studies. Thus, fixed effect model was used for conducting the analysis. Taking the highest score or severe hypogammaglobulinemia incidence across the studies, the pooled incidence rate of hypogammaglobulinemia within 30 days was 0.299 (0.253 to 0.344) and 90 days was 0.337 (0.296, 0.377). Similarly, the pooled fixed effect model across the studies for neutropenia within first 30 days following CART therapy was 0.798 (0.777, 0.819), B-cell aplasia was 0.936 (0.908, 0.964) and lymphopenia was 0.864 (0.842, 0.887) as shown in figure 2.

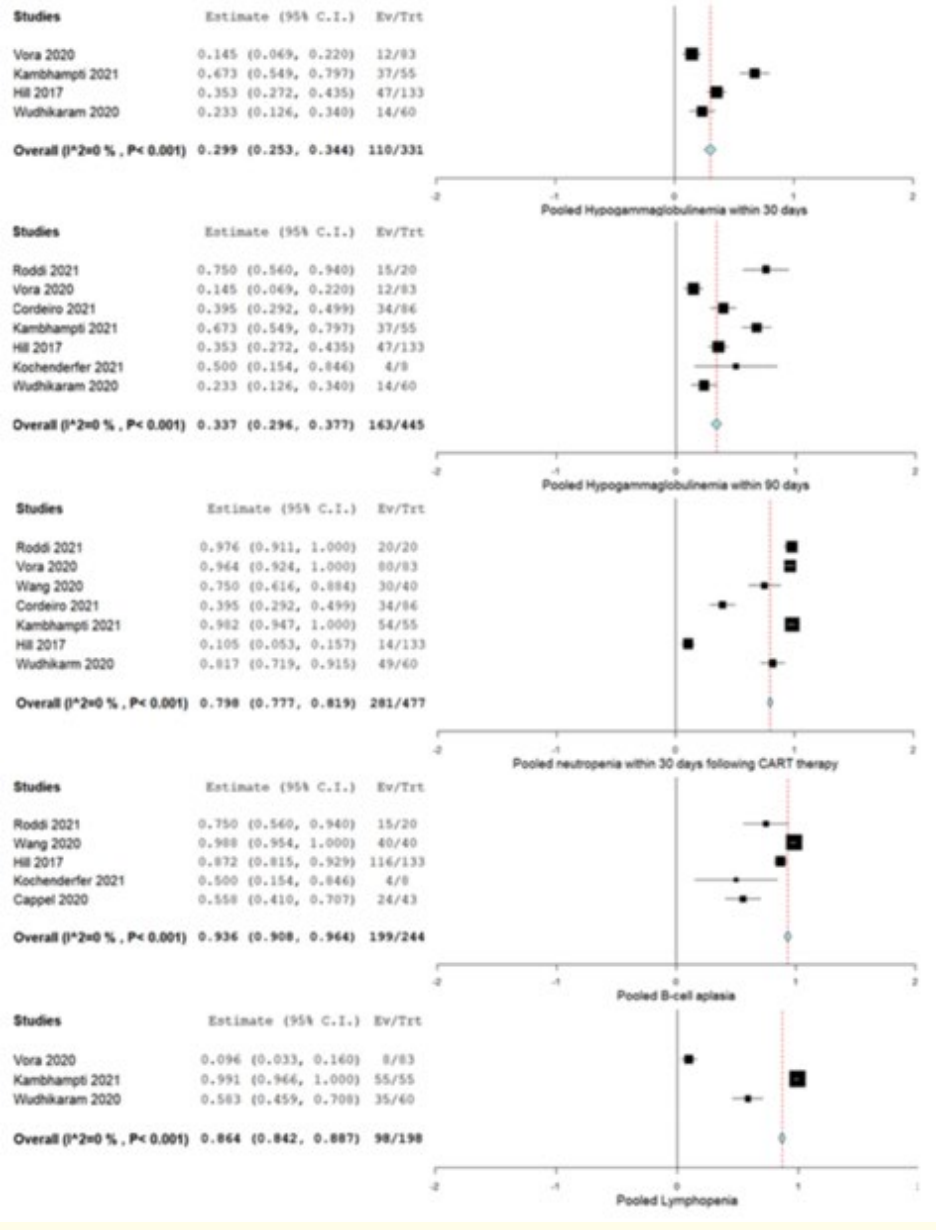

Figure 2: *Meta-analysis of A. Incidence of hypogammaglobulinemia for first 30 days, B. Incidence of hypogammaglobulinemia for first 90 days, C. Neutropenia within 30 days, D. B-cell aplasia and E. Lymphopenia.*

Discussion

This meta-analysis mainly focused on evaluating the incidence of hypergammaglobulinemia following CART therapy in haematological malignant patients. Previously no systematic review or meta-analysis was conducted that assessed the incidence of hypergammaglobulinemia for CART therapy. This review also focused on complications related to CART therapy, and probable treatment management options for hypogammaglobulinemia. Moreover, this meta-analysis also considered the quality assessment of different studies, but no such sensitivity analysis or subgroup analysis was possible.

Overall, the incidence of hypogammaglobulinemia within 30 days of post CAR therapy was found to be 33.23% and 36.62% within the first 90 days. The meta-analysis conducted in this review used a fixed-effect model that showed significant pooled incidence of hypogammaglobulinemia within 30 days and 90 days. Our result on the incidence of hypogammaglobulinemia could not signify that there is a gradual decrease in hypogammaglobulinemia after 30 days of CART therapy. However, two studies suggested that there is a gradual decrease in hypogammaglobulinemia after 30 days [4,11]. In this review, the pooled incidence of neutropenia within the first 30 days was 59%. An increase in neutropenia is directly associated with an increase in infection [4].

The meta-analysis also suggested significant findings for neutropenia, B-cell aplasia, and lymphopenia after CART therapy. This signifies the high chances of getting infection initially within a few days of CART therapy. However, this review couldn't state the period taken for the decrease in neutropenia, lymphopenia, and B-cell aplasia as is suggested in previous retrospective studies. The review was also able to state the criteria for Hypergammaglobulinemic patients across different studies. Most of the studies included criteria for Hypogammaglobulinemia as patients having IgG antibodies less than 400 mg/dl, but in one study, the criteria of hypogammaglobulinemia were IgG < 800 mg/dL, IgM < 50 mg/dL, and IgA < 100 mg/dL [12]. Further, this review rightly identified the management of hypogammaglobulinemia by injecting IgG antibodies intravenously. Following CART therapy, there was a decrease in IgG, IgM, and IgG antibodies, and IgM is the first to recover in the blood serum. Hypogammaglobulinemia following CART therapy can persist for a long time even after B-cell recovery. Thus, patients with moderate to severe hypogammaglobulinemia were advised to continue the IgG for a longer period [12]. Two studies in this review reported a decrease in infection after 29 days following CART therapy [4,11]. Prior and subsequent therapy also plays an important role in the increase in infection such as HCT, cyclosporamide plus fludarabine, and hypogammaglobulinemia. Moreover, the incidence of infection and toxicity following CART therapy was observed more in adults than in younger children [4,11,12]. Tritiated CART therapy dose helps in the reduction of the disease burden but splitting the dose can result in delayed or discontinuation of the second dose and prolongation of toxicity [11].

In terms of methodology, the study had strengths and weaknesses. First, a systematic search followed by the screening of articles was done based on the pre-designed inclusion and exclusion criteria. Another key strength of the study was that quality checking of all the studies was conducted and taken into consideration while assessing the efficacy, but most of the studies were either low or fair quality. While on the other hand, all the steps of this review process were conducted by a single reviewer, and no authors were contacted during the review process. However, to minimize the bias, each and all steps were double-checked. Secondly, most of the studies were retrospective or prospective studies which were included in this review. According to the hierarchy of evidence RCT and clinical trials provide very good clinical evidence, but only two studies were clinical trials, and one was an open-label study [17].

Conclusion

Overall, there was a good amount of heterogeneity among the study design and study outcome. From the above evidence, it is well established that following CART therapy, hypogammaglobulinemia increases with a decrease in neutrophils, lymphocytes, and B-type cells.

Thus, the number of infective patients increases initially and slowly decreases. Most of the studies provided evidence on the management of hypogammaglobulinemia with IgG antibodies. The overall incidence of hypogammaglobulinemia within 30 days was 33.23%, and neutropenia complications following CART therapy were 59% but difficult to conclude as a greater number of good quality clinical trials are required reporting at the same time interval across all the studies. Moreover, larger sample size across studies are required to find the association between hypogammaglobinaemia and type of infection.

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