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REVIEW

Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine in patients with immunocompromising conditions: a review of available evidence

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ABSTRACT

Immunocompromising conditions increase the risk of invasive pneumococcal disease (IPD). Vaccine uptake in patients with these conditions may be low in part because of concerns about decreased immunogenicity and safety in these high-risk groups. We conducted a literature search to identify publications describing antibody responses to 13-valent pneumococcal conjugate vaccine (PCV13) in immunocompromised individuals recommended for PCV13 vaccination by the US Advisory Committee on Immunization Practices (ACIP). This review summarizes immunogenicity data from 30 publications regarding the use of PCV13 comprising 2406 individuals considered at high risk for IPD by the ACIP. Although antibody responses to PCV13 in individuals with immunocompromising and high-risk conditions were variable and generally lower compared with healthy controls, the vaccine was immunogenic and was largely well tolerated. Based on these findings, concerns regarding immunogenicity and safety of PCV13 are not supported and should not be barriers to vaccination in high-risk populations.

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PCV13; invasive pneumococcal disease; vaccination; immunocompromised; high-risk; immunogenicity

1. Introduction

Streptococcus pneumoniae is a major cause of serious diseases, including meningitis and pneumonia.[1] Individuals with weakened immune systems are at higher risk for pneumococcal infection, associated hospitalizations, and related mortality compared with healthy individuals.[2-6] Some estimates show over one quarter of all cases of invasive pneumococcal disease (IPD) occur in immunocompromised individuals, with the highest risk occurring among individuals with hematological malignancies.[5] Studies have shown that individuals with multiple myeloma (MM) have the highest risk for IPD compared with individuals with other immunocompromising conditions, with the risk reported to be up to 176 times greater in patients with MM compared with immunocompetent individuals.[2-5] Individuals with sickle cell disease and chronic renal failure on dialysis have also been shown to be at 25 and 19 times greater risk of IPD than immunocompetent individuals, respectively.[5] Another study estimated that adults with HIV infection had an IPD incidence 49 times higher than individuals without HIV; moreover, infection reoccurrence is up to 9 times more frequent in HIV-infected individuals.[7-8]

Two vaccines are available in the United States to prevent pneumococcal disease. The 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13®/Prevenar 13®, Pfizer Inc, Philadelphia, PA) contains pneumococcal capsular polysaccharides 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to a nontoxic diphtheria protein CRM_{197}.[9] Chemical linkage to a carrier protein stimulates a T cell–dependent response.[10] The 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax® 23, Merck and Co., Inc., Whitehouse Station, NJ) contains 12 of the serotypes included in PCV13 (all but 6A) plus serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F; capsular polysaccharides in this vaccine are unconjugated and stimulate a T cell–independent response that does not induce immunological memory.[11-13]

Since June 2012, the US Advisory Committee on Immunization Practices (ACIP) has been recommending the use of PCV13 in addition to PPSV23 in individuals ≥19 y of age with underlying conditions perceived as a high risk for IPD, including functional or anatomic asplenia, cerebrospinal fluid (CSF) leaks, cochlear implants, and specified immunocompromising conditions (Table 1). In February 2013, the routine use of PCV13 for individuals with the same high-risk conditions was also recommended in children aged 6 to 18 y.[14]

Despite the increased risk of IPD among immunocompromised individuals, immunization rates in this high-risk population remain low. Available surveillance reports show that only 23% of adults (19–64 y of age) at increased risk, including immunocompromised individuals, ever received a pneumococcal vaccine.[17] Possible reasons include lack of health-care provider knowledge about vaccine recommendations and appropriate timing of vaccination relative to disease treatment; uncertainty about potential vaccine benefit in an immunocompromised host; and safety concerns, such as allograft rejection.[18-21]

Concerns regarding low vaccine effectiveness may stem from the stated possibility of impaired ability of immunocompromised individuals to mount an antibody response to vaccination and limited awareness of the amount of immunogenicity data for PCV13 in diverse patients with immunocompromising conditions.[9] The objective of this review is to summarize current data on PCV13 vaccination

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Table 1. Underlying medical conditions for which both PCV13 and PPSV23 are currently recommended by ACIP for individuals ≥6 y of age.[14-16]

Risk group	Underlying medical conditions
Immunocompetent	• Cerebrospinal fluid leak • Cochlear implant
Functional or anatomic asplenia	• Sickle cell disease/other hemaglobinopathy • Congenital or acquired asplenia
Immunocompromised	• Congenital or acquired immunodeficiency • HIV infection • Chronic renal failure • Nephrotic syndrome • Leukemia • Lymphoma • Hodgkin disease • Generalized malignancy • Iatrogenic immunosuppression • Solid organ transplant • Multiple myeloma

ACIP = Advisory Committee on Immunization Practices; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

in patients with immunocompromising and other high-risk conditions included in the ACIP PCV13 recommendation.

2. Methods

Searches in Ovid MEDLINE, Ovid Embase, and Derwent Drug File were conducted to identify PCV13 publications describing antibody responses in individuals with high-risk conditions. Searches were performed on July 12, 2018. Database searches were limited to the following dates: Ovid MEDLINE® without Revisions: 1996 to July Week 1 2018; Ovid MEDLINE® In-Process & Other Non-Indexed Citations: July 12, 2018; Derwent Drug File: 1964 to 2018 Week 27; Embase: 1974 to July 12, 2018; Ovid MEDLINE® Epub Ahead of Print: July 12, 2018. Search terms included all relevant terminology for the 7-valent pneumococcal conjugate vaccine (PCV7) and PCV13 (e.g., "prevnar 7," "prevenar 7," "pneumococcal 7-valent," "pneumococcal heptavalent," or "CRM197," "diphtheria CRM 197 protein," "prevnar 13," "pneumococcal 13-valent," "pneumococcal tridecavalent," respectively) and the following high-risk conditions included in the ACIP recommendation for PCV13 vaccination: sickle cell disease (SCD), other hemoglobinopathy, congenital asplenia-SCD, acquired asplenia (splenectomy), HIV, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, and MM. No limitations were placed on study design or setting. Search results were manually evaluated for relevance to the topic of PCV13 effectiveness in patients with these conditions. For search results for underlying conditions that returned PCV13 and PCV7 articles, only PCV13 articles were selected; for search results that returned no PCV13 articles, PCV7 articles were selected. Search results of abstracts later published as full articles were included as full articles.

3. Results

A total of 184 articles were identified by the literature search and reviewed for eligibility; of these, 30 publications describing studies of PCV13 use in individuals with conditions included by ACIP vaccination recommendation were eligible for inclusion. In total, 2406 individuals with immunocompromising conditions were included in this review, including those with congenital or acquired asplenia/SCD (four articles; n = 277), HIV infection (eight articles; n = 1025), hematologic disorders (eight articles; n = 534), autoimmune/rheumatologic disorders (seven articles; n = 487), solid organ transplant (two articles; n = 66), and chronic renal failure (one article; n = 17).[22-50] No studies of PCV13 use were identified in individuals with cochlear implants, nephrotic syndrome, congenital or acquired immunodeficiencies (other than HIV infection), CSF leaks, Hodgkin disease, or generalized malignancy. Although two of the identified studies evaluated PCV7 use in children with idiopathic nephrotic syndrome or cochlear implants, these were not included here to limit the focus to PCV13.[51,52]

Studies used a combination of assays, primarily (i) opsonophagocytic (OPA) assays – which are used to measure the functional activity of antibody titers in vivo – and/or (ii) immunoglobulin G (IgG) assays, which measure the concentrations of serotype-specific antibodies circulating in sera. These assays are used to assess protective immunity following vaccination.[53,54] The endpoints for immune response are presented for study populations as OPA geometric mean titers (GMTs) and/or IgG geometric mean concentrations (GMCs). In infants, the World Health Organization (WHO) recognizes a population-based threshold of ≥0.35 μg/mL for serotype-specific IgG following pneumococcal conjugate vaccine administration for use in the evaluation of new PCVs.[55] There is no defined protective threshold in adults, for whom functional antibody assessment via OPA is favored.[55,56] Included studies used a variety of endpoints to assess vaccine responses and were grouped according to medical condition; these are summarized in Table 2 and described below.

3.1. Congenital or acquired asplenia/sickle cell disease

Two studies investigated the immunogenicity of one dose of PCV13 in asplenic adults with thalassemia major and a history of pneumococcal vaccination, including receipt of one to four doses of PPSV23.[23,24] In both studies, IgG GMCs were significantly increased following PCV13 vaccination. In the first study by Papadatou and colleagues, 39 patients aged 19 to 48 y received PPSV23 at 1 to 11 y before PCV13 and PCV7 at 7 y before PCV13.[23] Previous PPSV23 vaccination had a dose- and time-dependent effect on PCV13 immunogenicity and immunologic memory. Specifically, a positive correlation was observed between both IgG and IgM memory B cells and IgG antibodies elicited by PCV13 and the time elapsed since last PPSV23 vaccination; a negative correlation was observed between memory B cell and antibody levels and the number of PPSV23 doses. In the second study by Rezai and colleagues, PCV13 and PPSV23 were administered 8 weeks apart in 47 individuals aged 20 to 44 y who had received PPSV23 >5 y previously.[24] IgG GMCs elicited by PCV13 were significantly greater when PCV13 was administered before versus after PPSV23. These data are supportive of the general recommendations for administering PCV13 before PPSV23.[15]

In another study by Nived and colleagues, PCV13 immunogenicity in 33 splenectomized adults was investigated; the most common reasons for splenectomy were trauma or

Table 2. Overview of studies.

Reference	Purpose of study	Study design	Country/ Setting	Study population			Main outcomes	
				Vaccination history	N[a]	Age,[b] y	Immunogenicity	Safety
Asplenia/sickle cell disease								
Papadatou et al.[23]	Immunogenicity (serotypes 3, 9V, 19A, 19F, and 23F only) of one dose of PCV13 in patients previously vaccinated with PPSV23	Prospective cohort; immunogenicity evaluated 7 and 28 d postvaccination	Greece/ Academic hospital	PCV7 vaccination 7 y prior; 1–4 doses of PPSV23 1–11 y prior	39	36.5 (19–48)	PCV13 induced serotype-specific increases in IgG antibody GMCs in previously vaccinated subjects. Reduced immunogenicity among subjects previously vaccinated with PPSV23 was time and dose dependent.	NR
Rezai et al.[24]	Immunogenicity of one dose of PCV13 and one dose of PPSV23	Randomized crossover; immunogenicity evaluated 8 weeks after second vaccination	Iran/ Academic hospital	Vaccination with any pneumococcal vaccine >5 y prior	47	29.6 (20–44)	Mean IgG concentrations were significantly higher in subjects receiving PCV13 before vs after PPSV23.	NR
Nived et al.[25]	Immunogenicity (12 serotypes common with PPSV23 only) of one dose of PCV13	Prospective cohort; immunogenicity evaluated 4–6 weeks postvaccination	Sweden/ Community hospital	PCV13 naive and PPSV23 naïve or >1 y prior; or PPSV23 <1 y prior if two or more serotype-specific IgG concentrations were <0.35 µg/mL	33	52 (22–80)	Serotype-specific IgG GMCs were higher in subjects receiving prior PCV13 and PPSV23 vs PPSV23 alone. PCV13 induced a booster response in those with previous PPSV23 vaccination.	NR
De Montalembert et al.[22]	Immunogenicity and safety of two doses of PCV13	Open-label, single arm, phase 3; immunogenicity evaluated 1 month postvaccination	France, Lebanon, United Kingdom, United States, Egypt, Italy, Saudi Arabia/NR	one or more doses dose of PPSV23 administered ≥6 months prior	158	13.3 ± 3.08	PCV13 elicited serotype-specific increases in IgG GMCs and OPA GMTs against all vaccine serotypes after one dose. Responses were generally comparable after each dose.	PCV13 was well tolerated and safety events were consistent with those previously reported for PCV13; no new safety concerns emerged during the study. Most AEs and SAEs were vaso-occlusive crises.
HIV infection								
Bhorat et al.[27]	Immunogenicity and safety of three doses of PCV13 followed by one dose of PPSV23	Open-label, single arm, phase 3 study; immunogenicity evaluated 1 month postvaccination	South Africa, Romania/NR	Pneumococcal vaccine-naive	301	25.8 ± 16.7	One dose of PCV13 elicited significant increases in serotype-specific IgG GMCs and OPA GMTs compared with prevaccination. For most serotypes, IgG GMCs modestly increased with subsequent doses of PCV13 and after PPSV23.	PCV13 and PPSV23 were well tolerated; no new safety concerns emerged during the study.
Glesby et al.[26]	Immunogenicity and safety of three doses of PCV13	Open-label, single arm, phase 3; immunogenicity evaluated 1 month postvaccination	United States/ Medical centers	One or more doses of PPSV23 administered ≥6 months prior	329	47.3 (19–73)	One dose of PCV13 elicited significant increases in serotype-specific IgG GMCs and OPA GMTs in PPSV23-prevaccinated subjects. For certain serotypes, antibody responses modestly increased with subsequent doses.	Rates of injection site redness and swelling and headache, fatigue, and vomiting after dose 3 were slightly higher in subjects who received two or more vs one previous dose of PPSV23.
Lombardi[30]	Immunogenicity and safety of two doses of PCV13 vs one dose of PPSV23	Prospective cohort with control group; immunogenicity evaluated 8, 24, and 48 weeks postvaccination	Italy/ Infectious disease clinical centers	Pneumococcal vaccine-naive	100	PCV13, 43.9 ± 9.05; PPSV23, 45.6 ± 10.5	At 48 weeks, serotype-specific IgG GMCs were comparable for PCV13 and PPSV23.	PCV13 and PPSV23 were well tolerated; no new safety concerns emerged during the study.

(*Continued*)

Table 2. (Continued).

Reference	Purpose of study	Study design	Country/ Setting	Study population			Main outcomes	
				Vaccination history	N[a]	Age,[b] y	Immunogenicity	Safety
Sadlier et al.[28]	Immunogenicity (12 serotypes common with PPSV23 only) of prime-boost immunization with PCV13 followed by PPSV23 vs PPSV23 alone	Randomized; immunogenicity evaluated 8 and 28 weeks postvaccination	Ireland/ Ambulatory HIV clinic	NR	60	37 ± 10	Serotype-specific IgG GMCs and OPA GMTs (for select serotypes) increased following a prime-booster strategy with PCV13/ PPSV23 vs PPSV23 alone.	NR
Ohtola et al.[31]	Immunogenicity (serotypes 14 and 23F only) of one dose of PCV13 followed by PPSV23 8 weeks later vs PPSV23 alone	Prospective cohort; immunogenicity evaluated 1 month postvaccination	United States/ Academic hospital	PPSV23 >5 y prior or vaccine-naive	51	PPSV23, 55.2 (50–64); PCV13/PPSV23/HIV+, 54.8 (49–63); PCV13/PPSV23/HIV–, 55.6 (50–64)	Serotype-specific increases in IgG GMCs after PCV13/PPSV23 vs PPSV23 alone were similar. Immunogenicity in HIV+ PCV13/ PPSV23 recipients was decreased compared with HIV-negative–matched controls.	NR
Ohtola et al.[32]	Immunogenicity as measured by serotype-specific (serotypes 14 and 23F only), total, and switched memory B cells of one dose of PCV13 followed by PPSV23 8 weeks later vs PPSV23	Prospective cohort; immunogenicity evaluated 1 week postvaccination	United States/ Academic hospital	PPSV23 >5 y prior or vaccine-naive	48	PPSV23, 55.0 (51–59)[c]; PCV13/PPSV23/HIV+, 54.0 (52–58)[c]; PCV13/PPSV23/HIV–, 55.5 (52–58)[c]	For HIV+ subjects, serotype-specific B cell concentrations were significantly lower with PCV13/PPSV23 vs PPSV23 alone.	NR
Rossheim et al.[29]	Immunogenicity (serotypes 3, 6A, 7F, and 19A only) of one dose of PCV13 in subjects with PPSV23 vaccination 1–3 vs >3 y prior	Prospective observational cohort; immunogenicity evaluated 1 month postvaccination	United States/HIV clinic	PPSV23 1–3 y and ≥3 y prior	96	44 (20–65)	Fold rise in serotype-specific IgG GMCs (serotypes 3, 7F, 19A) increased in subjects with a longer interval since PPSV23 vaccination.	NR
Farmaki et al.[13]	Immunogenicity and immunologic memory (serotypes 3 and 14 only) of one dose of PCV13 followed by one dose of PPSV23 12 months later in patients taking antiretroviral therapy	Prospective study; immunogenicity evaluated 1 month after each vaccination	Greece/ Community hospital	PCV13-naive, PPSV23 vaccination >1 y prior	40	50.6 ± 8.6	Significant increases in serotype-specific IgG antibody concentrations were observed after combined vaccination (2-fold rise-fold rise observed 1 month after PCV13 vaccination alone). Significant increases in serotype-specific memory B cells[d] were observed after PCV13 vaccination.	NR
Hematologic malignancies (leukemia, lymphoma, multiple myeloma)								
Pasiarski et al.[33]	Immunogenicity of one dose of PCV13 in treatment-naive patients with CLL vs healthy subjects	Prospective cohort with control group; immunogenicity evaluated 1 month postvaccination	Poland/ Community hospital	Pneumococcal vaccine-naive	39	CLL, 66 (47–79); control, 68.5 (54–83)	Antibody response (≥2-fold increase in serotype-specific IgG antibody concentrations compared with prevaccination) was reported in 58.3% of patients with CLL and 100% of healthy subjects.	NR
Svensson et al.[34]	Immunogenicity and safety of one dose of PCV13 vs PPSV23 in treatment-naive patients with CLL	Two-arm, randomized; immunogenicity evaluated 1 month postvaccination	Sweden/ Hematology units	Pneumococcal vaccine-naive or pneumococcal vaccination >5 y prior	128	69 (46–87)	OPA GMTs elicited by PCV13 were higher than those elicited by PPSV23 for 10 of 12 serotypes common to both vaccines.	38% of patients reported AEs, all of which were grades I or II. No vaccine-related SAEs were reported.

(*Continued*)

Table 2. (Continued).

Reference	Purpose of study	Study design	Country/ Setting	Study population			Main outcomes	
				Vaccination history	N[a]	Age,[b] y	Immunogenicity	Safety
Andrick et al.[35]	Immunogenicity of one dose of PCV13 in patients with CLL ± concomitant ibrutinib	Prospective cohort; immunogenicity evaluated 1 month postvaccination	United States/ Academic hospital	Pneumococcal vaccination >2 y prior	8	69.5 (53–77)	Antibody responses (≥2-fold increase in postvaccination serotype-specific IgG antibody concentrations over baseline levels of three serotypes) were observed in all patients with CLL who were not treated with ibrutinib and none of those who were.	NR
Small et al.[40]	Immunogenicity (serotypes 1, 3, 4, 6B, 7F, 14, 18C, 19F, and 23F only) and safety of three doses of PCV13 in HSC recipients	Prospective cohort; immunogenicity evaluated after reaching pre-set immunologic milestones (T cell and Ig thresholds)	United States/ Academic hospital	NR	59	39 (3–68)	Antibody response (seroconversion or 3-fold rise in serotype-specific IgG antibody concentrations) was 73%, including 87% of patients aged <21 y at HCT and 67% of patients aged >21 y. Response correlated with higher levels of circulating CD4+, CD45RA+ T cells and CD27 +, IgM– memory B cells.	No SAEs were observed.
Bahuaud et al.[37]	Immunogenicity (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F only) of one dose of PCV13 in patients with MM	Prospective cohort; immunogenicity evaluated 1, 6, and 12 months postvaccination	France/ Community hospital	Pneumococcal vaccine-naive	20	62 (50–74)	At 1 month post-vaccination, 12 (60%) patients were responders by IgG GMCs (>2-fold increase from baseline and >1 µg/mL antibody concentration) and eight were responders by OPA (>4-fold increase from baseline and titer ≥LLOQ). At 6 and 12 months, only six and two responders, respectively, had persistent immunity by OPA responder criteria.	NR
Locke et al.[36]	Immunogenicity (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19, and 23F only) and safety of up to three doses of PCV13 in patients with MM receiving autologous hematopoietic cell transplant	Prospective cohort; immunogenicity evaluated 3 months post-transplant	United States/ Academic hospital	NR	6	Adults	All patients who received pre- and post-transplant vaccinations were responders by IgG levels (significantly greater fold changes in PCV13 serotype-specific IgG titers compared with non-PCV13 serotype IgG levels).	PCV13 was well tolerated and safety events were consistent with those previously reported for PCV13. No new safety concerns emerged during the study.

(*Continued*)

Table 2. (Continued).

Reference	Purpose of study	Study design	Country/ Setting	Study population			Main outcomes	
				Vaccination history	N[a]	Age,[b] y	Immunogenicity	Safety
Cordonnier et al.[39]	Immunogenicity and safety of four doses of PCV13 followed by one dose of PPSV23 in HSC recipients	Prospective cohort; immunogenicity evaluated 1 month after each dose	Europe, Canada, United States/NR	No pneumococcal vaccination since HSC transplant	216	42.0 (2–71)	Serotype-specific IgG GMCs and OPA GMTs increased in all patients after dose 1. IgG GMCs and OPA GMTs increased after dose 4 compared with after dose 3 (except for serotype 3 IgG GMCs in the pediatric group). Immunity remained stable after PPSV23 administration. Pediatric patients tended to have numerically higher GMCs than adults after each PCV13 dose and after PPSV23.	Local and systemic reactions were more frequent after dose 4 vs dose 3 of PCV13. Six possible vaccine-related SAEs were reported: facial diplegia (14 d after PCV13 dose 1), injection site erythema and pyrexia (1 d after PCV13 dose 2), two episodes of autoimmune hemolytic anemia in a single patient (18 and 116 d after PCV13 dose 3), Guillain-Barré syndrome (29 d after PCV13 dose 4 and 1 d after PPSV23), and cellulitis (2 d after PPSV23).
Shah et al.[38]	Immunogenicity (serotypes 14, 19F, and 23F only), incidence, time to vaccination, and safety for three doses of PCV7/ PCV13 with 1–2 booster doses (for nonresponders)	Retrospective cohort; immunogenicity evaluated after dose 3 and 1–2 booster dose(s) 1 month apart	United States/ Academic hospital	NR	58	34 (0.9–64)	30 (53%) patients achieved a serotype-specific IgG response (seroconversion or ≥3-fold rise in GMCs) to all three serotypes (serotypes 14, 19F, 23F). Among initial nonresponders who were revaccinated one or more doses all evaluated subjects responded.	PCV13 was well tolerated; no new safety concerns emerged during the study.
Autoimmune/rheumatologic disorders								
Kantso et al.[41]	Immunogenicity (12 serotypes common with PPSV23 only) and safety of one dose of PCV13 or PPSV23 in patients with Crohn disease ± concomitant immuno-suppressive drugs	Randomized clinical study; immunogenicity evaluated 1 month postvaccination	Denmark/ Academic hospital	Pneumococcal vaccine-naive	151	44 ± 14	Serotype-specific IgG GMCs were higher for PCV13 compared with PPSV23 and highest in the untreated group. Immune responses were impaired for patients on azathioprine or mercaptopurine ± TNF-α antagonist therapy.	Safety events were consistent with those reported previously; no new safety concerns emerged during the study.
Rakoczi et al.[42]	Immunogenicity and safety of one dose of PCV13 in patients with RA ± concomitant DMARD therapy (ETA vs ETA+MTX)	Prospective cohort with control group; immunogenicity evaluated 1 and 2 months postvaccination	Hungary/ Academic hospital	Pneumococcal vaccine-naive	46	RA, 55.1 ± 10.4; control, 63.9 ± 9.8	IgG antibody concentrations significantly increased from pre- to 1 and 2 months postvaccination in RA and control groups and remained higher than baseline levels at 8 weeks postvaccination. Immune responses were significantly higher in the control groups not receiving ETA or ETA/MTX.	No clinically relevant AEs were reported in any patients.

(*Continued*)

Table 2. (Continued).

Reference	Purpose of study	Study design	Country/ Setting	Study population			Main outcomes	
				Vaccination history	N[a]	Age,[b] y	Immunogenicity	Safety
Kapetanovic et al.[47]	Immunogenicity (serotypes 6B and 23F only) of one dose PCV13 in patients with RA ± concomitant MTX	Prospective cohort; immunogenicity evaluated 4–6 weeks postvaccination	Sweden/ Academic hospital	Pneumococcal vaccine-naive	20	MTX, 67.4 (39.1–78.6); no DMARD, 67.3 (38.6–86.7)	Antibody responses (≥2-fold increase in postvaccination serotype-specific IgG antibody concentrations over baseline levels) was significant for 6B in the MTX treated group (evident in one patient only) and both 6B and 23F in the non-treated group.	NR
Caporuscio[45]	Immunogenicity and safety of one dose of PCV13 in patients with RA on immunosuppressive therapy vs healthy controls	Prospective cohort with control; immunogenicity evaluated 1 and 6 months postvaccination	Italy/ Academic hospital	NR	44	RA, 62.1 ± 11; control, 63.7 ± 2	Postvaccination, 61% of patients receiving DMARDs had an antibody response (≥2-fold increase in antibody titer); protection was maintained through 6 months.	Mild systemic and local AEs (redness and/or swelling of injection site) were reported by 44% of vaccinated patients with RA and by 16% of healthy subjects.
Nived et al.[43]	Immunogenicity (serotypes 6B and 23F only) and safety of one dose of PCV13 in patients with systemic vasculitis ± immunosuppressive therapy	Prospective cohort with control; immunogenicity was evaluated at 4–6 weeks postvaccination	Sweden/ Academic hospital	Pneumococcal vaccine-naive or PPSV23 >1 y prior	98	Vasculitis, 65 (22–85); control, 57 (17–85)	Serotype-specific IgG GMCs and the proportion of patients with IgG concentrations ≥1 µg/mL increased in all groups postvaccination but were lower in the vasculitis group compared with the control. Pre- and postvaccination OPA titers were lower in vasculitis patients compared with controls.	PCV13 was well tolerated; no new safety concerns emerged during the study.
Nagel et al.[44]	Immunogenicity (12 serotypes common with PPSV23 only) and safety of one dose of PCV13 in patients with SLE ± belimumab and/or DMARD therapy vs healthy controls	Prospective cohort with control group; immunogenicity evaluated 4–6 weeks postvaccination	Sweden/ Academic hospital	Pneumococcal vaccine-naive or pneumococcal vaccination >5 y prior	68	SLE, 50.8; control, 43.6	Serotype-specific IgG GMCs increased significantly in patients with SLE and controls postvaccination, but IgG titers and fold increases were significantly lower among patients. No significant differences in postvaccination IgG GMCs or in fold increases were observed in belimumab-treated patients.	PCV13 was well tolerated; no new safety concerns emerged during the study.
Winthrop et al.[46]	Immunogenicity and safety of one dose of PCV13 in patients with moderate to severe psoriasis using tofacitinib	Open label vaccine substudy; immunogenicity evaluated 4 weeks postvaccination	United States/ Academic hospital	Pneumococcal vaccine-naive	60	52 (23–70)	GMFRs from baseline in serotype-specific OPA titers ranged from 8.3 to 101.9. GMTs ranged from 4.9 to 99.5 at baseline and from 66.1 to 2782.2 at 4 weeks.	37.7% of patients reported treatment-emergent AEs; no severe AEs or SAEs were reported.
Solid organ transplant								
Dendle et al.[49]	Immunogenicity and safety of one dose of PCV13 in kidney transplant recipients; measurement of donor-specific (anti-HLA) antibodies	Prospective cohort; immunogenicity evaluated 1 month postvaccination	Australia/ Outpatient vaccination clinic	Pneumococcal conjugate vaccine-naive; 77% had prior PPSV23	45	56.1 (47.0–63.9)	Median increases in IgG GMCs from baseline ranged from 1.1- to 1.7-fold across the 13 serotypes included in PCV13; all patients had OPA GMTs ≥1:8 for three of four serotypes tested by this method.	PCV13 was well tolerated; no new safety concerns emerged during the study. No anti-HLA antibodies or transplant rejections were reported.

(*Continued*)

Table 2. (Continued).

				Study population			Main outcomes	
Reference	Purpose of study	Study design	Country/ Setting	Vaccination history	N[a]	Age,[b] y	Immunogenicity	Safety
Sun et al.[48]	Immunogenicity (serotypes 6B, 14, 19F, 23F only) and safety of one dose of PCV13 in solid organ transplant candidates and recipients	Prospective cohort; immunogenicity evaluated 1 month postvaccination	Taiwan/Academic hospital	NR	21	NR	At 1 month postvaccination, 58.3–75.0% of 13 patients with follow-up had significant antibody responses (≥2-fold increase in antibody levels from baseline) to each of the individual serotypes.	PCV13 was well tolerated; no new safety concerns emerged during the study.
Renal failure								
Mitra et al.[50]	Immunogenicity and safety of one dose of PCV13 in patients with ESRD receiving dialysis	Prospective cohort; immunogenicity evaluated 2 months and 1 y postvaccination	United States/ Academic hospital	Pneumococcal vaccination naive or >5 y prior	17	62.6 ± 9.05	Serotype-specific IgG GMCs were significantly increased for all serotypes at 2 months postvaccination compared with prevaccination. By 1 y, significant increases were evident only for serotypes 5, 6B, 18C, and 19F. Vaccine responses (≥2-fold increase in antibody concentration and concentration ≥1 µg/mL) to >75% of serotypes was shown in 53% at 2 months and 23.5% at 12 months postvaccination.	PCV13 was well tolerated; no new safety concerns emerged during the study.

AE = adverse event; CLL = chronic lymphocytic leukemia; DMARD = disease-modifying anti-rheumatic drug; ESRD = end-stage renal disease; ETA = etanercept; GMC = geometric mean concentration; GMFR = geometric mean fold rise GMT = geometric mean titer; GVHD = graft vs host disease; HLA = human leukocyte antigen; HSC = hematopoietic stem cell; Ig = immunoglobulin; LLOQ = lower limit of quantitation; MM = multiple myeloma; MTX = methotrexate; N/A = not applicable; NR = not reported; OPA = opsonophagocytic assay; PCV7 = 7-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; RA = rheumatoid arthritis; SAE = serious adverse event; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor

[a]Vaccinated subjects.

[b]Median (range) or mean ± SD, unless stated otherwise.

[c]Median (interquartile range).

[d]Refers specifically to isotype-switched Ig memory B cells.

abdominal surgery due to a benign process. Increased IgG GMCs for serotypes 1, 3, 4, 5, 7F, 18C, 19A, 19F, and 23F were observed following PCV13 vaccination in asplenic individuals who had received previous vaccination with one, two, or three doses of PPSV23 (92% of participants had not received PPSV23 within the previous 12 months), suggesting that PCV13 is immunogenic for these serotypes when used as a booster dose in asplenic patients previously vaccinated with PPSV23.[25]

A study by De Montalembert and colleagues investigated the immunogenicity and safety of two doses of PCV13 administered approximately 6 months apart in 158 children (mean age, 13.3 y) with SCD who had received one or more doses of PPSV23 ≥6 months earlier. Statistically significant increases in IgG GMCs and OPA GMTs were observed after a single dose, with similar GMCs observed after doses 1 and 2. One year after the second PCV13 vaccination, OPA GMTs were significantly higher than pre-PCV13 levels for all 13 vaccine serotypes, and IgG GMCs were significantly higher for all 13 serotypes except for serotypes 3 and 5. No relationship between the time interval between PPSV23 and PCV13 administration and antibody responses to PCV13 was identified. Overall, PCV13 was well tolerated.[22]

3.2. HIV infection

Eight studies examined antibody responses after pneumococcal vaccination in HIV-infected individuals. Two phase 3 clinical studies assessed the immunogenicity and safety of a three-dose PCV13 series, and four studies compared prime-boost PCV13 or PCV13/PPSV23 vaccination with PPSV23-only vaccination.[26-28,30-32] One study evaluated PCV13 responses at various intervals after PPSV23 vaccination, and another evaluated responses to PCV13 followed by PPSV23 vaccination.[13-29]

3.2.1. PCV13 three-dose regimen

Both open-label, single-arm, phase 3 studies of PCV13 immunogenicity and safety in HIV-infected individuals evaluated serotype-specific IgG and OPA responses 1 month after vaccination.[26,27] In both studies, participants received stable highly active antiretroviral therapy (HAART) for at least 6 weeks prior to the first vaccination or did not receive antiretroviral therapy. In the first study by Bhorat and colleagues, 301 vaccine-naive PCV13 recipients (mean age, 25.8 y) received at least one of three PCV13 doses 1 month apart followed by one PPSV23 dose. After one dose, PCV13 elicited significantly increased antibody responses for PCV13 serotypes compared with prevaccination; however, for most serotypes, antibody responses increased modestly with subsequent doses of PCV13 and after PPSV23. Safety events were generally mild and did not increase with the number of PCV13 doses.[27] In the second study by Glesby and colleagues, 329 subjects aged 19 to 73 y previously vaccinated with one or more doses of PPSV23 ≥6 months earlier received at least one of three doses of PCV13 administered 6 months apart. The first PCV13 dose elicited a significant antibody response to all vaccine serotypes with only modest increases after subsequent doses.[26] Rates of injection-site redness and swelling as well as fatigue, headache, and vomiting after dose 3 were slightly higher in subjects who had received two or more previous PPSV23 doses compared with those who had received one dose.[26] In both studies, the second and third doses only provided incremental antibody increases compared with the response after the initial dose of PCV13.[26,27] These findings support the current ACIP recommendation of a single dose of PCV13 in HIV-positive adults.[16]

3.2.2. PCV13 prime-boost versus PPSV23-only regimen

Lombardi and colleagues compared a PCV13/PCV13 prime-boost schedule (8-week interval) with a single PPSV23 dose in 100 pneumococcal vaccine-naive HIV-infected adults aged 18 to 65 y, nearly all (99%) of whom received stable antiretroviral therapy; both vaccine groups showed similar GMCs for IgGs against the common antigens at 48 weeks postvaccination. There was no significant increase in IgG levels for eight of the 13 serotypes (serotypes 1, 4, 5, 6B, 14, 19A, 19F, 23F) after the second dose of PCV13. The percentage of participants achieving threshold IgG antibody concentrations was similar overall, but notably the percentage of responses to serotype 3 was significantly lower for thresholds of ≥1 μg/mL (at week 8) and ≥0.35 μg/mL (at week 48) for the PCV13 group. The IgG seroconversion rate was significantly higher only for serotype 6B at 24 weeks for the PCV13 group. Both vaccines were safe and well tolerated.[30]

A single-center study by Sadlier and colleagues compared the immunogenicity of a PCV13/PPSV23 prime-boost schedule (4-week interval) with that of PPSV23 alone in 60 pneumococcal vaccine-naive HIV-infected adults (mean age, 37 y), about half of whom were on HAART. Results showed substantially greater IgG and OPA responses in the prime-boost group for five serotypes (1, 3, 4, 19F, 23F) and three serotypes (14, 23F, 6A) at week 28, respectively, compared with those receiving PPSV23 only. Two-fold IgG responses and 4-fold GMT increases were also more frequently observed in the prime-boost group compared with the PPSV23-only group (70% vs 52%, $p < .01$ and 48% vs 36%, $p < .01$, respectively).[28]

An additional study by Ohtola and colleagues compared a PCV13/PPSV23 prime-boost schedule (8-week interval) with a single dose of PPSV23 in 51 HIV-infected adults aged 49 to 64 y (84% had PPSV23 >5 y prior) on antiretroviral therapy for ≥1 y; the PCV13/PPSV23 group was also compared with a PCV13/PPSV23 HIV-negative control group.[32] Among HIV-infected individuals, IgG and OPA responses to serotypes 14 and 23F were measured, showing similar increases after vaccination with PCV13/PPSV23 compared with PPSV23 alone, with no significant difference between the groups. Compared with HIV-negative individuals, HIV-infected individuals had reduced IgG responses to serotype 14 and reduced OPA responses to serotype 23F.[31] The authors also assessed B-cell responses through experimental assays, with results suggesting that PCV13 may not enhance responses to subsequent PPSV23 vaccination in older HIV-infected adults.[32] Serotype-specific B-cell responses were measured 1 week postvaccination after administration of PCV13 followed 8 weeks later by PPSV23 or PPSV23 alone in HIV-infected adults (aged 51–59 y) on antiretroviral therapy for ≥1 y. Serotype-specific B cell percentages were significantly

increased for only serotype 23F after PCV13 and for both serotype 23F and 14 after PPSV23 in the PCV13/PPSV23 group compared to prevaccination levels; significant increases occurred for both serotypes in the PPSV23-only group. Transmembrane activator and calcium-modulating cyclophilin ligand interactor-positive B-cell percentages were significantly lower in the PCV13/PPSV23 HIV-infected group compared with the PPSV23-only HIV-infected group.[32]

3.2.3. PCV13 after PPSV23

A study by Rossheim and colleagues in 96 HIV-infected adults aged 20 to 65 y receiving combination antiretroviral therapy evaluated the effect of time since PPSV23 receipt on antibody responses to subsequent PCV13 vaccination.[29] At 1 month after vaccination with PCV13, the foldrise in IgG GMCs for the three tested serotypes (3, 7F, 19A) was higher for individuals who received PPSV23 >3 y earlier compared with those who received PPSV23 between 1 and 3 y earlier, although only serotype 7F reached significance on univariate analysis. The authors suggested that receipt of PCV13 >1 y after PPSV23 may improve serologic responses to both vaccines in HIV-infected adults.[29]

3.2.4. PPSV23 after PCV13

Farmaki and colleagues evaluated the immunogenicity of one PCV13 dose followed by one PPSV23 dose 1 y later in 40 HIV-infected adults (median ± SD age, 50.6 ± 8.6 y) receiving antiretroviral therapy.[13] An approximately 2-fold rise in IgG antibody concentrations was elicited after PCV13 receipt across all patients for each of the two measured serotypes (serotypes 3 and 14), with a smaller increase after PPSV23. Antibody concentrations were 40% lower in the group with lower CD4+ T-cell counts (200–399 cells/μL). Immunologic memory was assessed by evaluating polysaccharide specific IgM+ memory B cells (IgM+ MBC) and isotype-switched immunoglobulin (sIg+ MBC). IgM+ MBC remained stable after PCV13 dosing; however, the IgM+ MBC pool was significantly reduced after PPSV23 dosing compared with baseline levels. In contrast, sIg+ memory B-cell counts were increased after PCV13 vaccination but had no increase after PPSV23 vaccination compared with baseline.[13]

3.3. Hematologic conditions

Eight studies evaluated responses to PCV13 in patients with hematologic malignancies, including leukemia, MM, and mixed hematological disorders.[33-40]

3.3.1. Leukemia

In one study by Pasiarski and colleagues involving patients with leukemia, one dose of PCV13 was assessed in 24 adults aged 47 to 79 y with treatment-naive chronic lymphocytic leukemia (CLL) and 15 healthy control subjects aged 54 to 83 y. All healthy subjects and 58.3% of patients with CLL responded to vaccination (i.e., ≥2-fold increase in serotype-specific IgG concentrations 30 d post-PCV13). A significant increase in the percentage of plasmablasts 7 d postvaccination was observed in both groups, indicating a rapid response to PCV13.[34] prospectively compared OPA GMTs following vaccination with either PCV13 or PPSV23 in 128 patients with CLL aged 46 to 87 y, finding that PCV13 elicited higher serotype-specific GMTs compared with PPSV23 for 10 of the 12 serotypes common to both vaccines (serotypes 1, 3, 4, 5, 7F, 9V, 18C, 19A, 19F, 23F) in addition to seven or more 6A; no differences were found for serotype 6B and 14. Positive responses (OPA titer greater than or equal to the lower limit of quantitation for seven or more serotypes) were more frequent after PCV13 vs PPSV23.[34] An additional study by Andrick and colleagues evaluated eight patients aged 53 to 77 y with CLL, four taking ibrutinib (a Bruton tyrosine kinase inhibitor for B cell malignancies, which is associated with increased risk of infection as a treatment side effect) and four control patients not receiving ibrutinib.[35-57] All control patients with CLL not taking ibrutinib met the defined antibody response to PCV13 (≥2-fold increase in postvaccination IgG concentrations for three or more serotypes), but responses were not observed in the four patients being treated with ibrutinib.[35]

3.3.2. Multiple myeloma

Two small studies led by Locke and Bahuaud assessed PCV13 vaccination in patients with MM. In the first, patients with MM undergoing autologous HCT were given PCV13: two patients received three doses (pretransplant and at 7–10 and 21–24 d following transplant); three patients received two doses (pretransplant and at d 21 post-transplant); and one patient received a single dose (pretransplant).[36,37] All patients who received pre- and post-transplant PCV13 vaccinations showed significantly greater IgG antibody responses against vaccine-specific serotypes compared with nonvaccine serotypes. There was a significant increase in serotype-specific IgG levels when compared with prevaccination levels for 6 of the 11 serotypes tested (3, 4, 6B, 9V, 18C, 23).[36] The other study assessed a single dose of PCV13 in 20 patients aged 57 to 75 y with smoldering (i.e., early) MM. Immunogenicity was assessed for PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) at 1 month, 6 months, and 12 months post-vaccination.[37] One month post-PCV13, 12 patients responded based on IgG levels measured in an enzyme-linked immunosorbent assay (ELISA; i.e., >2-fold increase in IgG antibody concentration and concentration ≥1 μg/mL for more than five serotypes) and eight patients responded based on OPA (titer greater than or equal to the lower limit of quantitation and 4-fold increase from baseline for more than five serotypes). When persistent immunity was assessed at 6 months postvaccination, seven patients were responders based on the ELISA (IgG) criteria and six based on OPA. This decreased to five responders based on ELISA (IgG) criteria and two responders based on OPA criteria after 12 months.[37]

3.3.3. Hematopoietic stem cell transplant recipients

An open-label study by Cordonnier and colleagues investigated the immunogenicity and safety of a four-dose PCV13/one-dose PPSV23 vaccination schedule in 216 individuals aged 2 to 71 y with different hematologic disorders who had received allogeneic HCT 3 to 6 months previously.[39] Subjects received the first three PCV13 doses at 1-month intervals, the fourth dose 6 months later, and the single PPSV23 dose

1 month thereafter. IgG antibody concentrations and OPA titers increased significantly for all 13 vaccine serotypes from baseline to after the third dose of PCV13. Responses declined during the interval between PCV13 doses 3 and 4 and then increased from pre- to postdose 4; little change was observed after PPSV23. Local and systemic adverse events (AEs) were more frequent after PCV13 dose 4, but the overall safety profile of the four-dose PCV13 schedule was considered acceptable.[39]

Shah and colleagues evaluated responses to PCV13 (or its precursor, PCV7) in 58 cord blood transplantation recipients aged 0.9 to 64 y undergoing treatment for hematologic malignancies. Among these 58 patients, 24 received PCV7, 33 received PCV13, and one patient received both vaccines.[38] Following three doses of PCV13 (or PCV7 if available at the time; doses 1 month apart and administered ≥6 months post-cord blood transplantation), 52% (30/58) of patients responded (i.e., >3-fold rise in IgG GMC) to all three pneumococcal serotypes tested (14, 19F, 23F) and 33% (19/58) responded to one or two of the three serotypes tested. A total of 16% (9/58) of patients did not respond to any tested serotypes; of these, six patients were revaccinated with one or two booster doses but only five patients were evaluated. All five evaluated patients who initially did not respond to primary vaccination did so when revaccinated with one or two booster doses. Response rates did not differ between children and adults. No significant differences were noted between vaccine responses and prior chemotherapy, graft versus host disease, or low dose immunosuppression therapy.[38]

A study by Small and colleagues evaluated responses to three doses of PCV13 in 59 hematopoietic stem cell transplant (HCT) recipients aged 3 to 68 y, most of whom had undergone transplantation for leukemia or myelodysplastic syndrome.[40] Immunization was performed upon immune competency milestone achievements (i.e., >200 CD4 cells/μL and IgG levels >500 mg/dL at ≥6 weeks without gammaglobulin). Overall, 73% of patients responded to PCV13 (i.e., >3-fold rise in titer to specified pneumococcal serotypes), including 87% of patients aged <21 y and 67% of patients aged >21 y.[40]

3.4. Autoimmune/rheumatologic disorders

Seven studies assessed PCV13 in patients with diverse underlying medical conditions who were taking various immunosuppressive drugs to treat immunologic disorders.[41-47]

A study by Kantsø and colleagues compared antibody responses to PCV13 and PPSV23 in 151 patients (mean age, 44 y) with Crohn disease in the presence or absence of immunosuppressive drugs containing azathioprine (AZA) or mercaptopurine (immunomodulators associated with increased infection susceptibility) and tumor necrosis factor (TNF)-α antagonist therapy.[41] One month postvaccination, serotype-specific IgG GMCs were higher for PCV13 compared with PPSV23 (significantly greater for five serotypes); overall increases were highest in untreated patients (significantly greater in PCV13 compared to PPSV23 for four serotypes). Immunity, while impaired, was induced in both immunosuppressive drug-treated patients and patients treated with immunosuppressive drugs along with TNF-α antagonists; PCV13 responses in these groups were significantly greater than PPSV23 for three and two serotypes, respectively.[41]

Two other studies also compared PCV13 antibody responses in patients with rheumatoid arthritis (RA) on immunosuppressant therapy to responses in patients with the same or a similar disease who were not taking immunosuppressants.[42,47] In the study by Rakoczi and colleagues, patients with RA (median age, 55.1 y) treated with etanercept (ETA; a TNF-α inhibitor associated with serious lung infections, including pneumonia) or a combination of ETA and methotrexate was compared to controls. Serotype-specific IgG antibody concentrations significantly increased (≥2-fold increases) from pre- to 1 and 2 months post-vaccination in all groups, but those on drug therapy had significantly lower PCV13 antibody responses compared with untreated patients (median age, 63.9 y).[42-58] The other study by Kapetanovic and colleagues evaluated 10 patients with RA on methotrexate compared to 10 patients with RA not on disease-modifying antirheumatic therapy (DMARD).[47] Immunogenicity was assessed 4–6 weeks postvaccination for two vaccine serotypes (6B and 23F). Patients on methotrexate showed a significant increase in 6B IgG GMCs postvaccination, likely as a result of a dramatic response from a single patient. Patients not on therapy had a significant increase to both serotypes tested.[47]

Three studies compared PCV13 responses in immunosuppressed patients with those in healthy controls and found that PCV13 antibody responses were generally higher in healthy individuals.[43-45] Caporuscio and colleagues compared 24 patients with RA on low dose glucocorticoids, methotrexate, and/or anti-TNF therapy to three healthy controls. One month postvaccination, 61% of patients developed a positive response (2-fold increase in concentration) to the 13 serotypes.[45] Mild local and systemic AEs were more frequently reported in immunosuppressed patients with RA compared with healthy individuals (44% vs 16%, respectively).[45] Another study by Nived and colleagues evaluated IgG concentrations for serotype 6B and 23F in patients on treatment for vasculitis compared to controls. Treatment included AZA, methotrexate, cyclophospharmide, mycophenolate mofetil, prednisolone, rituximab, and TNF inhibitors in a variety of therapy combinations. Patients were stratified into two groups based on treatment. Both the patient groups and the control group had increases in IgG GMCs to the two serotypes tested (6B and 23F) postvaccination with no difference between groups in the proportion achieving a response (2-fold increase in IgG).[43] The proportion of patients with IgG concentrations ≥1.0 μg/mL also increased across both patients and controls. Both the patient groups and control group had postvaccination increases in OPA titers for serotype 23F; however, responses were lower in patients on treatment.[43] Finally, Nagel and colleagues compared immune responses of 47 patients with systemic lupus erythematosus (SLE) on therapy (mean age, 50.8 y) with those of 21 healthy controls (mean age, 43.6 y).[44] Therapy included various combinations of AZA and other DMARDs, hydroxychloroquine, prednisolone, and belimumab. IgG GMCs increased significantly for all 12 serotypes tested (1, 3, 4, 5, 6B, 7F, 9V, 14, 18 C, 19A, 19F, 23F) in patients with SLE and controls postvaccination, but the response was significantly lower in those with than in controls. There were

no differences noted in the antibody response of the belimumab-treated patients compared with those who received other therapies.[44]

A single-arm study by Winthrop and colleagues evaluated the geometric mean fold rise from baseline in serotype-specific OPA titers for the 13 PCV13 serotypes 4 weeks after immunization in patients with severe to moderate psoriasis receiving immunosuppressive therapy.[46] Sixty patients aged 23 to 70 y with psoriasis treated with tofacitinib, a Janus kinase inhibitor, were included. GMTs ranged from 4.9 to 99.5 at baseline and from 66.1 to 2782.2 after 4 weeks. More than 80% of patients achieved measurable serotype-specific OPA titers for each serotype.[46]

3.5. Solid organ transplantation

Two publications reported outcomes of PCV13 in solid organ transplant (SOT) recipients.[48,49] In one study by Dendle and colleagues, a prospective cohort of 45 clinically stable kidney transplant recipients (median time since transplant, 2.24 y) aged 47.0 to 63.9 y received a single PCV13 dose.[49] The majority (81%) of patients were on tacrolimus + mycophenolate + prednisolone therapy. Antipneumococcal IgG antibodies were measured for the 13 vaccine serotypes pre- and 1 month postvaccination, and OPA antibody titers were measured for four serotypes postvaccination. Median increases in antipneumococcal IgG GMCs were 1.1- to 1.7-fold for all 13 serotypes, and OPA GMTs were ≥1:8 for three of the four serotypes tested (1, 4, 9V, 23F). No transplant rejections, de novo anti-HLA antibody development, or IPD episodes occurred during the 12-month postvaccination period.[49] The second study by Sun and colleagues was described in a conference abstract and assessed the immunogenicity and safety of a single PCV13 dose in two heart transplant recipients and 19 SOT candidates.[48] At 1 month postvaccination, 58.3% to 75.0% of 13 patients who were followed up showed anticapsular antibody responses (i.e., ≥2-fold increase compared with baseline) to the four pneumococcal serotypes tested (6B, 14, 19F, 23F).[48]

A case report described by Gupta and Brennan discussed the occurrence of PCV13-associated immune thrombocytopenic purpura in a 77-y-old renal transplant recipient (summarized here, but not part of the 30 studies included in Table 2).[59] The patient presented approximately 1 month after PCV13 vaccination with bruising at insulin injection sites; following methylprednisolone, immunoglobulin, and platelet transfusion treatment, the patient's blood counts improved to baseline within a month and remained stable thereafter.[59]

3.6. Renal failure

A single study by Mitra and colleagues assessed the immunogenicity of PCV13 in 17 older adults (median age, 62.6 y) with end-stage renal disease receiving dialysis.[50] Among the 17 patients analyzed, 11 had received prior pneumococcal vaccination (>5 y previously). IgG GMCs increased significantly compared to baseline for all 13 serotypes at 2 months and four serotypes (5, 19F, 6B, 18C) remained higher at 12 months after vaccination. Vaccine responses (i.e., ≥2-fold increase in IgG concentration and absolute post-PCV13 IgG concentration ≥1 μg/mL) to >75% of the PCV13 serotypes were observed in nine of the 17 patients at 2 months postvaccination and in four patients at 12 months after vaccination.[50]

4. Discussion

To our knowledge, this is the first review to focus exclusively on studies evaluating PCV13 immunogenicity in patients with immunocompromising conditions. A 2014 review summarized the efficacy and safety of available pneumococcal vaccines (PPSV23, PCV7, and PCV13) in immunocompromised patients, but more data have since become available.[60] The studies summarized herein included patients with diverse underlying medical conditions, covering the majority of conditions specified for coverage in the ACIP recommendations for PCV13 vaccination.[16]

Overall immunogenicity findings support that patients, despite an underlying condition or immunosuppressive treatment regimen, generally mounted antibody responses against the serotypes contained in PCV13 following a single dose. Results from multiple studies suggest that a second or third dose in HIV-infected populations may not provide additional benefit in terms of increases in antibody levels.[26,27]

In individuals who had undergone hematopoietic bone marrow transplantation, four doses of PCV13 were evaluated.[39] As expected, individuals with an underlying condition or therapy that can cause immunosuppression tended to have lower antibody responses to PCV13 compared with healthy counterparts; however, these individuals are also at high risk for pneumococcal disease. Immune responses varied by condition, serotype, and type of antibody response measured; most of these data were derived from open-label studies. These findings are consistent with the results of PCV7 use in immunocompromised individuals.[61]

The ACIP recommends that individuals with immunocompromising conditions receive PCV13 followed by PPSV23 at least 8 weeks later to offer broader protection against the high burden of IPD these individuals face.[14,16] The rationale behind the sequence of PCV13 followed by PPSV23 is based on studies that demonstrated a better response to serotypes included in both vaccines if PCV13 was administered first.[15] At the time of the ACIP recommendation, data on the immunogenicity of PCV13 in immunocompromised individuals were not available.[16] As this current review shows, there are now PCV13 immunogenicity data in this population. Overall, findings generally support the ACIP recommended PCV13/PPSV23 vaccine sequence in immunocompromised individuals and further reinforce the importance of administering the conjugate vaccine first.[13,24,27,28,32,39]

PCV13 was generally well tolerated, and safety events were consistent with those previously reported, such as redness, swelling, and injection-site pain.[9] No new safety concerns emerged during the studies.[26,39,44,45]

This review is limited by variability in designs, size, and endpoints of the currently available studies. A more complete understanding of PCV13 use and the ACIP recommended PCV13/PPSV23 sequence in immunocompromised individuals will emerge as more clinical studies are conducted and real-world usage data are examined. It should be noted that

three of the studies included in this review were published as conference abstracts rather than expanded, peer-reviewed publications, limiting the data available. In other cases, patient groups were too small to draw robust conclusions, patient therapies varied within groups, and prevaccination histories were not always available.[40,45,48] The use of immunosuppressive drugs makes it difficult in some cases to extrapolate PCV13 immunogenicity results from patients with a specific medical condition to the treatment of patients with another condition and/or treatment.

Finally, the collective interpretation of all studies included in this review should be considered with the understanding that endpoints used across studies to measure immunogenicity differed. ELISAs are widely used to measure IgG levels to evaluate vaccine immunogenicity because they are generally easier to perform and are easily scalable.[56] Some studies utilized the threshold of IgG antibody concentrations ≥0.35 μg/mL, a widely accepted population-based level for use in the evaluation of PCVs after an infant series; others utilized an IgG threshold of ≥1 μg/mL.[55,56] Responders were often quantified as achieving a 2-fold rise in pre- to postvaccination concentrations. However, no clear threshold IgG antibody concentration or foldrise has been established to indicate protection or efficacy in an individual, and IgG results may not always correlate with functional activity, particularly in adults.[37,56] OPA titer is a preferred measure of vaccine immunogenicity in adults because it directly measures functional activity (the ability of antibodies to opsonize and kill bacteria), and therefore adult studies employing OPA endpoints are expected to generate more reliable results.[56] However, as with the IgG, there is no OPA titer that has been established as a protective threshold. Additional variability among the conclusions of studies in this review may be related to inconsistency among the subsets of serotypes evaluated in each experiment.

Vaccine efficacy trials with PCV13 in immunocompromised patients are not currently available. A recent study demonstrated a vaccine effectiveness of 72.8% for PCV13 against hospitalized vaccine-type community-acquired pneumonia in adults over the age of 65 y.[62] In this real-world population, approximately 46% of the patient population had an immunocompromising condition or a condition otherwise defined in the review as high risk, and the vaccine effectiveness did not change substantially when adjusting for risk group.

Randomized, controlled efficacy trials of pneumococcal conjugate vaccines to demonstrate protection against IPD are not feasible. Results from these immunogenicity studies provide valuable support for the use of PCV13 in immunocompromised individuals for whom PCV13 vaccination is recommended because of their increased risk of pneumococcal disease.[16] Concerns regarding a poor safety profile or the lack of immunogenicity of PCV13 are not supported by data and should not create barriers to appropriate pneumococcal immunization in this patient population.

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EC, RI, BS-T, WW, MMM, and DS are employees of Pfizer and may hold stock and/or stock options. All authors approved the final article.

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