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Use of Cytokine Therapy in Primary Immunodeficiency

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Abstract Of the six cytokine therapies approved by the US Food and Drug Administration, five of them have been used in patients with primary immunodeficiency (PID). In some applications, clear benefits have been demonstrated, while in others, effects have been more marginal. The most compelling current applications of cytokine therapy in PID are those of granulocyte colony stimulating factor in severe congenital neutropenia and interferon gamma in chronic granulomatous disease. Despite encouraging results with interleukin-2 in common variable immunodeficiency and select other indications, its use in PID is not widespread.

Keywords Cytokine · Therapy · Primary immunodeficiency · Granulocyte macrophage colony stimulating factor (GM-CSF) · Granulocyte colony stimulating factor (G-CSF) · Interferon alpha (IFN-α) · Interferon gamma (IFN-γ) · Interleukin-2 (IL-2)

Introduction

Cytokines are critical soluble messengers of the immune system and have been exploited therapeutically. In this review, the clinical uses of the US Food and Drug Administration (FDA)-approved cytokines as they have been applied to primary immunodeficiency (PID) will be addressed. There are five FDA approved cytokines, which will be discussed: (1) granulocyte macrophage colony stimulating factor (GM-CSF); (2) granulocyte colony stimulating factor (G-CSF or GCSF); (3) interferon alpha (IFN-α); (4) IFN-γ; and (5) interleukin-2 (IL-2). These cytokines and their FDA-approved indications are listed in Table 1. Only two cytokines are approved by the FDA for use in PID: G-CSF for severe congenital neutropenia (SCN) and IFN-γ for chronic granulomatous disease (CGD).

G-CSF stimulates production of neutrophils and other granulocytes from bone marrow. There are three forms of recombinant human G-CSF (rhG-CSF): Filgrastim (Neupogen), lenograstim, and PEG-filgrastim (Neulasta). The polyethelene glycol (PEG) form has a longer half-life, reducing the necessity of daily injections [1, 2]. GM-CSF functions as a leukocyte growth factor and stimulates production of granulocytes and monocytes. It is available in two forms: molgramostim and sargramostim (Leukine). IFN-γ induces and enhances antigen presentation, activates intracellular killing, and promotes T-cell differentiation [3]. IFN-α has direct antiviral properties through the induction of inherent cell antiviral proteins and programs. It also has a wide array of immunostimulant properties and is most commonly utilized in the treatment of viral diseases including those caused by hepatitis B or C viruses or human papilloma virus. Recombinant formulations include interferon alfacon-1 and interferon alpha 2a and are commonly administered as pegylated forms [4]. IL-2 was discovered as a T-cell growth factor [5] but has a wide range of effects on diverse T-cell subsets and natural killer (NK) cells. Although it is only FDA approved for malignant melanoma and renal cell carcinoma, it has been used in many diseases including, but not limited to, neuroblastoma, cutaneous T-cell lymphoma, breast cancer, and HIV. Each of the aforementioned cytokines has been administered to patients with PID. The

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Table 1 FDA approved cytokines and indications

Cytokine	Product name	FDA indication[a]	Manufacturer
Granulocyte macrophage colony stimulating factor (GM-CSF)	Leukine (sargramostim)	Following: Chemotherapy for AML Autologous PBMC transplant Autologous and allogeneic BMT Failure or Engraftment Delay Myeloid reconstitution	Berlex Labs/Bayer HealthCare Pharmaceuticals
Granulocyte colony stimulating factor (G-CSF)	Neupogen (Filgrastim)	**SCN** Cancer patients receiving myelosuppressive chemotherapy Chemotherapy for AML Cancer patients receiving BMT During PBMC collection and therapy	Amgen
Interferon alfacon-1	Infergen	Chronic HCV	Intermune Pharms/Valeant Pharmaceuticals International
Interferon alpha-2A	Roferon	Chronic HCV Hairy cell leukemia AIDS related Kaopsi's samcoma CML	Roche
Interferon alpha-2B	Intron A	HBV Hairy cell leukemia Malignant melanoma Follicular lymphoma Condylomata acuminata AIDS related Kaposi's sarcoma	Schering
Peginterferon alpha-2A	Pegasys	Chronic HCV Chronic HBV	Roche
Peginterferon alpha-2B	PegIntron	Chronic HCV	Schering
Interferon gamma-1B	Actimmune	**CGD** Osteopetrosis	Intermune Pharmaceuticals/Valeant Pharmaceuticals International
Interleukin-2 (IL-2)	Proleukin (Aldesleukin)	Metastatic melanoma Metastatic renal cell carcinoma	Chiron/Novartis

[a] These represent our best interpretation of FDA approved indications. For more detailed information, please see product labeling. Indications in bold indicate a primary immunodeficiency (PID)

AML acute myelogenous leukemia, *BMT* bone marrow transplantation, *CGD* chronic granulomatous disease, *CML* chronic myelogenous leukemia, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *PBMC* peripheral blood mononuclear cells, *SCN* severe chronic neutropenia

specific uses and the individual experiences in PID are summarized in Table 2 and reviewed below.

G-CSF and GM-CSF

SCN is an FDA approved indication for G-CSF. SCN results from the impaired bone marrow differentiation of the myeloid lineage leading to an absolute neutrophil count (ANC) below 200/μl. This leads to a susceptibility to recurrent and serious pyogenic bacterial infections [6]. Several studies have confirmed the safety and efficacy of G-CSF to increase ANC in SCN. In an initial study, an increase in ANC was demonstrated in two subpopulations after 8 days of therapy. The first group had an oscillating ANC with decreased superoxide (SO) and cytochrome b559 (n=4). The second group had a constant ANC and normal SO and cytochrome levels (n=3). Improvement in severe chronic gingivostomatitis, periodontis, oral ulcers, and interdental bone mineralization were identified within 1–6 months of therapy. Overall, therapy increased circulating neutrophils and improved morbidity despite variations in neutrophil functions among the subjects [7]. In a phase I/II clinical trial of both rhGCSF and rhGM-CSF for SCN, therapy with rhGM-CSF resulted in an absolute granulocyte increase in four subjects due to an increase in eosinophils. In contrast, treatment with rhG-CSF increased ANC greater than 1,000/μL in all subjects. No severe bacterial infections occurred during therapy with either factor, and all tolerated therapy with the exception of one receiving the highest dose of GM-CSF who

Table 2 Clinical applications of cytokines in patients with primary immunodeficiency

Cytokine	PID	Objective	Number of patients	Effect of treatment	AE/tolerability	Notes	Reference
G-CSF	SCN	Improve severe chronic gingivostomatitis	7	Improvement in: Periodontitis Oral ulcers ANC		Group 1: (n=4) Oscillating ANC Decreased SO and cytochrome b559 Group 2: (n=3) Constant ANC Normal SO and cytochrome levels	[7]
G-CSF and GM-CSF	SCN	Increase ANC	5	GM-CSF: ANC increase was due to eosinophils in 4 subjects	Well tolerated except one subject developed cutaneous necrotic vasculitis at the highest dose of rhGM-CSF	Phase I/II clinical trial	[8]
		Safety/Tolerability		G-CSF: All subjects had an increase in ANC>1000/μL			
G-CSF	SCN	Increase ANC	41	Improvement in:	Mild splenomegaly	Open Label Randomized Phase III trial	[9]
		Evaluate efficacy		ANC (>1,500 cells/μL) Infections Gingivitis Mouth ulcers			
G-CSF	SCN	Improve Infections	120	Improvement in: Mature neutrophils on bone marrow Infections Antibiotic use	Splenomegaly Bone pain Headache Rash		[10]
G-CSF	Kostmann's Syndrome	Increase ANC	5	Improvement in:	Medullary pain	Phase I-II study of rhG-CSF	[13]
		Improve Infections		Infections IV Antibiotic use ANC within 8–9 days (>1,000 cells/μL) Mature neutrophils on bone marrow	Splenomegaly Elevated Leukocyte Alkaline Phosphatase		

Table 2 (continued)

Cytokine	PID	Objective	Number of patients	Effect of treatment	AE/tolerability	Notes	Reference
G-CSF	Cyclic Neutropenia	Increase ANC	6	Improvement in: ANC Neutrophil turnover Cycle length Oropharyngeal inflammation Fever Infections			[18]
G-CSF	Cyclic Neutropenia	Treat pulmonary abscess, gingivitis, stomatitis, fever	1	Improvement in: ANC nadir Cycle length Infections Gingivitis			[19]
G-CSF	Myelokathexis (WHIM Syndrome)	Increase ANC Improve infections Increase IgG/IgA	2	Improvement in: Subject 1: ANC Normalization of IgA Infections Subject 2: ANC Normalization of IgG	Subject 1: Severe bone pain required discontinuation of treatment Subject 2: His mother stopped treatment and he developed bilateral pneumonia 2 months later	ANC increased within 4-8 hours as opposed to Kostmanns (rise within 8-9 days)	[20]
G-CSF	Myelokathexis (WHIM Syndrome)	Increase ANC	1	Improvement in: ANC within 4 h of treatment, highest at 24 h	Subject initially received GM-CSF (molgramostom) but developed hypersensitivity and was switched to G-CSF (Filgastrim and Lenograstim) without difficulty		[24]

G-CSF	HIGM and NK cell deficiency	Increase ANC	1	Improvement in: ANC Infections NK cell number			[27]
G-CSF	HIGM	Increase ANC	1	Improvement in: ANC Infections			[28]
G-CSF	HIGM	Increase ANC Treat severe oral and esophageal candidiasis	1	Improvement in: ANC Gingivostomatitis Antibiotic requirement Duration of hospitalization	Subject did well 22 months after discontinuation of G-CSF		[29]
G-CSF	XLA	Increase ANC Improve Infections	1	Improvement in: ANC after 4 days (>1,500 cells/mm^3)		Administered with IVIG	[30]
G-CSF	CGD	Treat liver abscess	1	No clinical improvement of liver abscess		Large improvement in eosinophils No change in NBT, SO production or cytochrome b content	[32]
IFN α-2b	XLP	Treat HCV and EBV	1	Clearance of HCV-RNA and EBV DNA	Well tolerated No lymphoma	Administered with ribavarin	[34]
Pegylated IFN α-2a/Ribavarin	CVID	Treat HCV	1	Improvement in: Liver function tests HCV RNA	Well tolerated	Liver transplantation and splenic embolization prior to therapy	[35]
IFN α-2b	ICD4L	Treat disseminated giant molluscum contagiosum (MC)	1	Eradication of MC		Continues to have recurrent infections	[36]
IFN α- 2b	HIES	Treat intractable MC	1	Eradication of MC without reoccurrence	Well tolerated		[38]

Table 2 (continued)

Cytokine	PID	Objective	Number of patients	Effect of treatment	AE/tolerability	Notes	Reference
IFN α- 2b	HIES	Treat oral papilloma	1	Improvement of oral papilloma		Recurrent sinopulmonary infections and new lesions continue to occur	[39]
IFN α-2b	HIES	Treat eczema	1	Improvement in eczema	Well tolerated except for fatigue and influenza like syndrome	Decreased number of circulating CD23+cells after treatment Decrease in serum IgE	[40]
IFN α	HIES	Treat resistant eczema	1	Stable clinical improvement		Normalization of in vitro T-cell cytokine production	[41]
IFN α	HIGM	Treat conjunctival MALT lymphoma	1	Complete regression of conjunctival lesions and symptoms		Topical application of IFN α Subject also had CHARGE syndrome	[42]
IFN α	XLA	Treat encephalitis	1	Clinical symptoms improved within one month of therapy		Unknown etiology of encephalitis despite thorough investigation Also received high dose IVIG	[43]
IFN-γ	HIES	Reduce IgE levels	5	Inhibition of IgE and IgG4 production	Minimal AE	This study was not designed to evaluate the efficacy of IFN-γ as a therapeutic modality in HIES	[44]
IFN-γ	HIES	Improve infections	1	Clinical improvement	IFN-γ triggered thrombocytopenia, increased serum antiplatelet antibody and ANA	No effect on serum IgE	[45]
IFN-γ	HIES	Treat tuberculous brain abscess	1	Improvement in: Oral fungal infection Mycobacterial brain infections		Decrease in serum IgE	[46]
IFN-γ	HIES	Improve atopic disease	1	Disease severity score improved from 11 to 3 in 20 weeks			[47]
rIFN-γ	CGD	Improve infections Evaluate long term safety and effectiveness	30	Improvement in: Serious infection by 67%	Well tolerated		[48]

rIFN-γ	CGD	Improve infections Evaluate long term safety and effectiveness	28	Improvement in: Median infection free time (993 days)	No deaths	12 month DBRCT study No effect on SO production and phagocyte staphylococcal killing	[49]
IFN-γ	CGD	Decrease frequency of infections Evaluate efficacy	128	Improvement in: Serious infection by 70% in both XL and AR CGD	Well tolerated	DBRCT study No effect on SO production	[50]
IFN-γ	CGD	Long term clinical safety and efficacy	76	Improvement in serious infections	Fever	Phase IV uncontrolled open label follow up study	[51]
IFN-γ	CGD	Evaluate effect on oxidant generation		No improvement in: -NADPH oxidase function			[52] [53]
IFN-γ	XL CGD and HIES	Improve infections Evaluate effect on oxidant generation	1	Clinical improvement No effect on respiratory burst		McLeod Phenotype (kell negative)	[54]
IFN-γ	XL CGD	Evaluate effect on oxidant generation	4	Improvement in: SO production Cytochrome b			[55]
IFN-γ	XL SCID	NTM	1	Regression of infection	Tolerated haploid identical BMT without rejection at 6 months of age		[57]
IFN-γ	Omenn's	Improve Infections Observe effect on cytokine profile	1	Normalization of eosinophils Improvement in: T-cell response to phytohemaglutinin Infections	Well tolerated and became a candidate for BMT	Down regulation of IL-5 and IL-10	[59]
IFN-γ	ICD4L	Cryptococcal Meningitis	2	Resolution of meningitis			[60]
IFN-γ	IFN gamma Receptor deficiency IL12p40 1L12Rβ1	NTM					[61] [62] [63]
IFN-γ	Partial recessive IFNγRI Deficiency	NTM	1	Regression of lesions		Subject had a homozygous hypomorphic mutation	[64]

Table 2 (continued)

Cytokine	PID	Objective	Number of patients	Effect of treatment	AE/tolerability	Notes	Reference
IL-2	SCID	Treatment after 2 failed bone marrow transplants	1	Improvement in: Clinical status T-cell proliferative response	Well tolerated for several years at home and has achieved normal growth parameters	Subject was deficient in IL-2	[67]
IL-2	WAS	Treat intractable herpes infection and chronic eczematoid dermatitis	1	Improvement in: Chronic eczematoid dermatitis	Well tolerated	During treatment CD3+ and CD4+ T-cell subsets increased	[70] [71]
IL-2	NEMO	Improve NK cell cytotoxicity	1	Improvement in: NK cell killing defect	Well tolerated		[73]
IL-2	CVID	Role as treatment option	15	Improvement in: Days of bronchitis, diarrhea and joint pain Proliferative responses to tetanus and *Candida* antigens		Compared to 39 controls with CVID for 12-18 months of therapy	[75]
IL-2	CVID	Role as treatment option	10	Reduces susceptibility of severe infections in the 6 months following treatment	Well tolerated	DBPC crossover study with natural human IL-2 in combination with IVIG IgG levels remained unchanged	[76]
IL-2	CVID	Role as treatment option	5	Improvement in: Infections Antibiotic requirements Ig secretion from B cells but no increase in serum IgG Prolonged T-cell helper activity		IV IL-2 conjugated to polyethylene glycol	[77]
IL-2	CVID	Role as treatment option	15	No improvement in: Chest x-ray or pulmonary function Serum Ig and lymphocyte markers Lymphocyte proliferation Antibody response to polysaccharide antigens	Well tolerated	Liposomal IL-2 formulation	[78]

IL-2	Combined ID (Nezelofs)	Observe in vitro T-cell responses	1	Improvement in: T-cell mediated cytotoxicity	Death due to pulmonary aspergillosis	May have had HIV although it was not confirmed by laboratory testing Subject had absence of endogenous IL-2 production	[10]
IL-2	Ataxia Telangiectasia	Treatment for pneumonia	1	Improvement in: Clinical status Response to T-cell mitogens Increases serum IgM, Restored B cell function in vitro	Well tolerated	Did not increase IgG levels Subject deficient in IL-2 production	[82]
IL-2	22q11.2 deletion	Correct inability of PBMC to proliferate to mitogens	1	Proliferative response to mitogens remained depressed Improvement in: T-cell counts	Death due to respiratory failure	HLA identical BMT or thymic transplantation was recommended	[84]
IL-2	ICD4L	Treat persistent and recurrent infections with deteriorating clinical condition	1	Improvement in: Mycobacterial disease CD4 cell counts B-cell counts T-cell proliferation			[85]
IL-2	ICD4L	Treat cryptococcus meningitis	1	Resolution of meningitis CD4+ cell count increased after 1 month of therapy			[86]
IFN-γ and GMCSF	Cyclic neutropenia	Treatment of resistant generalized verrucosis (HPV)	1	Improvement of warts	Well tolerated	HPV DNA undetectable 6 months after therapy	[87]
IL-2 and IFN-γ	CVID and abnormal CD8+ cell count	PML	1	IL-2 withdrawn due to widespread psoriaform rash	Clinical deterioration and death despite addition of IFN-γ	Treatment with IL-2 after weaning subject off corticosteroids post brain biopsy	[88]

developed cutaneous necrotic vasculitis [8]. Treatment of SCN in an open label randomized phase III trial of G-CSF in 41 subjects resulted in increased ANC >1,500/mm^3. This trial defined a marked reduction in infectious complications and resolution of gingivitis and oral ulcers, although mild splenomegaly was noted in a some patients [9]. Another phase III randomized control trial of rhG-CSF for SCN treated 120 subjects and lead to a 50% reduction in the incidence and duration of infection-related events and ~70% reduction in duration of antibiotic use. Splenomegaly, bone pain, headache, and rash, however, were reported as adverse events (AE) [10].

Kostmann's syndrome is a familial subtype SCN [11] and, recently, has been defined as resulting from mutation in the HAX1 gene [12]. An initial phase I/II study of five patients with Kostmann's syndrome treated with rhG-CSF identified increased ANC >1,000 cells/μL within 8–9 days. Each were treated for 9–13 months, and marrow aspirates demonstrated mature neutrophils. Neutrophil function assayed by the Rebuck-skin window demonstrated extravasation in four of five subjects during but not before treatment. Preexisting chronic infections resolved in most patients, and treatment reduced the incidence of new infections and need for intravenous antibiotics. Although morbidity was reduced, there were numerous AE limiting more widespread use of GM-CSF in this disease [13].

Another form of inborn and isolated neutropenia in which G-CSF has been studied is that of cyclic neutropenia. Cyclical neutropenia is characterized by periodic nadirs in the ANC and can be associated with susceptibility to pyogenic bacterial infection during periods of neutropenia [14–17]. G-CSF has been evaluated and found effective in two trials, which demonstrated significant increases in ANC. One trial described treatment-associated decreased length of neutropenic periods, increased neutrophil turnover, and decreased frequency of oral ulcers, as well as reduced fever and infections [18]. The other reported a single subject who had a higher ANC, reduced neutropenic periods, and improved gingivitis during treatment [19].

Myelokathexis is a rare congenital neutropenia resulting from impaired release of granulocytes from the bone marrow and occurs more commonly in women [20]. One form includes WHIM syndrome, which, in addition to myelokathexis, results in hypogammaglobulinemia and susceptibility to warts and respiratory tract infections [21, 22] and is due to mutation in the CXCR4 gene [23]. In a family with WHIM syndrome treated with G-CSF, both patients had increased ANC within 4–8 h (note the distinction to the kinetics of the effect compared to Kostmann's syndrome). Both patients also had normalization of humoral immune function but discontinued therapy due to bone pain [20]. G-CSF/GM-CSF therapy to improve ANC was also attempted in a female patient with myelokathexis. Therapy was performed initially with GM-CSF (molgramostim) and subsequently with G-CSF (filgrastim and lenograstim). All treatments normalized her ANC within 4 h, and the highest ANC was identified 24 h after administration. GM-CSF was discontinued in this subject due to hypersensitivity [24].

Although not a primary disorder of neutrophils, G-CSF has been studied in neutropenia occurring in the context of hyper-IgM syndrome (HIGM). HIGM results from impaired B-cell costimulation and leads to hypogammaglobulinemia, defective immunoglobulin class switch recombination, and somatic hypermutation [25]. Neutropenia is observed in as many as 60% of patients according to the US registry report [26]. There have been three separate reported cases of G-CSF administration for neutropenia in HIGM, and all demonstrated an increase in ANC and a reduction in the incidence of infection [27–29]. One patient was also noted to have an NK cell deficiency and had an increase in NK cell number after therapy [27]. Treatment resulted in an increase in ANC and NK cells and no further serious infections.

G-CSF has also been used in XLA, which is a characterized by lack of lymphoid tissue, bacterial sinopulmonary infections, and enteroviral infections of the central nervous system (CNS) and gastrointestinal tract [26]. One subject with XLA and neutropenia was treated with G-CSF in addition to intravenous immunoglobulin (IVIG) and antibiotics due to persistence of severe neutropenia. ANC improved after 4 days of treatment to >1,500 cells/mm^3 but subsequently fell after discontinuation. Ultimately, the patient's ANC recovered after the fifth IVIG infusion, indicating that G-CSF may be effective in the acute management of neutropenia in the context of XLA [30].

Finally, G-CSF has been utilized in CGD, which is characterized by recurrent bacterial and fungal infections with extraordinary susceptibility to life-threatening *Aspergillus* infection. The disease results from defects in the nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidase complex leading to aberrant SO generation in phagocytes [31]. A single patient with X-linked CGD was treated with G-CSF with the objective of improving a liver abscess. Although there was no improvement in the abscess, a large increase in white blood cells was seen (mostly comprised of eosinophils). Treatment did not result in a change in nitroblue tetrazolium (NBT) reduction, SO production, or cytochrome b content [32].

Interferon alpha

IFN-α was approved by the FDA for the treatment of hepatitis C virus (HCV) infection in 1986 and has been used successfully in the treatment of HCV in individuals who have

a PID. One example is in the X-linked lymphoproliferative syndrome (XLP): a PID characterized by immunoglobulin abnormalities as well as lymphoproliferation following Epstein–Barr virus (EBV) infection that results from mutations in the SHD2D1A gene [33]. IFN-α-2b was given to a 5-year-old patient with a SHD2D1A gene mutation who had EBV infection and had been previously infected with HCV via blood transfusion. The patient was treated with IFN-α-2b for 12 months in combination with ribavarin (RBV) and had no major AE. Undetectable levels of HCV RNA and EBV DNA were attributed to therapy. At age 18, levels were still undetectable, and he had no evidence of lymphoproliferative disease [34]. Pegylated IFN-α-2a/RBV was given to a 21-year-old man with common variable immunodeficiency (CVID) who contracted HCV from IVIG. Treatment was associated with clearance of HCV RNA and was well tolerated [35].

In addition to being used in treatment of hepatitis C, IFN-α has also been used to treat a variety of dermatologic conditions in patients with PID. A patient with idiopathic CD4+lymphocytopenia (ICD4L) and disseminated giant molluscum contagiosum (MC) resistant to imiquimod was treated with subcutaneous pegylated IFN-α-2b. After 16 months of therapy, eradication of lesions was reported, and no reoccurrence was noted for over 4 years [36]. IFN-α has also been used in patients with the hyper-IgE syndrome (HIES), which is characterized by recurrent staphylococcal abscesses, eczema, and elevated serum IgE levels [37]. A 9-year-old boy with HIES, severe eczema, and intractable MC was treated with subcutaneous IFN-α-2b for 6 months, and therapy was attributed with a dramatic reduction in his MC with no reported AE or lesion reoccurrence [38]. Widespread oral premalignant papillomas in a 7-year-old boy with HIES were treated with laser ablation followed by IFN-α-2b. This regimen resulted in improvement, but smaller and infrequent new lesions continued to occur. Sinopulmonary infections also continued [39]. Treatment of eczema in HIES with subcutaneous IFN-α demonstrated reductions in eczema, serum IgE levels, and circulating CD23+ cells [40]. This treatment was well tolerated except for fatigue and an influenza-like syndrome, but mild eczema returned 6 days after discontinuation of therapy [40]. A 7-month-old boy with HIES was treated with IFN-α-2b for recalcitrant eczema and pruritis [41]. A marked improvement in symptoms was noted 2 weeks after beginning therapy. Although serum IgE levels remained elevated without correlation to the clinical improvement, normalization of in vitro T-cell cytokine production was seen (reductions in IL-2, IFN-γ, IL-4, IL-5, IL-10, and TNF-α after 4 weeks of treatment). IgG production also slowly increased and normalized resulting in discontinuation of IVIG [41].

Topical IFN-α has also been used in 5-year-old child with coloboma, heart defects, choanal atresia, retarded growth, genital, and ear abnormalities (CHARGE) association and concomitant HIGM syndrome with the goal of improving an unusual conjunctival MALT lymphoma that was diagnosed in this patient. Complete regression of conjunctival lesions was reported, and recurrence was not identified over 1 year of observation [42]. A 6-year-old boy with XLA and encephalitis was treated with IFN-α and high-dose IVIG for 6 weeks with the objective of improving CNS disease. Although the etiology of the encephalitis was unknown, his symptoms improved within 1 month of therapy [43].

Interferon gamma

IFN-γ has been used in four separate single subjects with HIES. A first study focused upon IgE production after IFN-γ therapy in HIES demonstrated an inhibition of IgE and IgG4 production in vivo and in vitro with minimal AE. This study was not designed to evaluate the efficacy of IFN-γ as a therapeutic modality in HIES [44]. In a second study, however, IFN-γ treatment of HIES was implicated in triggering autoimmune thrombocytopenia via increased serum antiplatelet antibody and ANA. Infections and skin rashes improved, but there was no reported effect on serum IgE levels [45]. IFN-γ treatment was also used in a 7-year-old patient with HIES who developed lymphadenitis and brain abscess after receiving BCG vaccine at the age of 2 months. His disease course was not altered by conventional antimycobacterial treatment; however, IFN-γ treatment improved his brain abscess and reduced his serum IgE level [46]. An additional patient with HIES was treated with IFN-γ in an effort to alter atopic disease. Therapy was reported to have reduced the severity of the disease, although specific details were not provided [47].

Perhaps the most widespread use of cytokine therapy in PID has been for CGD. IFN-γ therapy is now an FDA-approved indication for CGD to reduce frequency and severity of infections and is supported by several studies. Treatment of 30 subjects demonstrated a reduction in serious infection by 67% with AE that included fever, diarrhea, and flu-like symptoms [48]. There were no obvious effects on growth and development in this study. A 12-month double-blind randomized placebo-controlled trial (DBRCT) of rIFN-γ in 28 CGD subjects demonstrated a median infection free time of 993 days without effect on SO production and phagocyte staphylococcal killing [49]. The largest DBRCT study of 128 subjects with CGD demonstrated rIFN-γ was well tolerated and decreased frequency of serious infections by 70% in both X-linked and autosomal recessive disease and without an effect on SO production [50]. An 8-year follow-up phase IV study suggested that IFN-γ prophylaxis for CGD is effective and well tolerated

over time [51]. Three separate studies, however, concluded that the clinical benefit of IFN-γ therapy is not accompanied by improvement in NADPH oxidase function [52–54]. This is in contrast to earlier studies, which described a long-lasting improvement in oxidative metabolism, bacterial killing, and cytochrome b content [55]. In selected patients having splice site mutations, IFN-γ therapy was demonstrated to increase splicing efficiency and production of functional protein [56]. It is important to note, however, that most studies with IFN-γ in CGD were performed before modern fungal prophylaxis was standard of care. Thus, results need to be interpreted with this in mind, and newer studies are indicated.

IFN-γ therapy has been utilized in a subject with X-linked severe combined immunodeficiency (SCID) and disseminated *Mycobacterium bovis* infection and resulted in regression of infection. The patient was then able to tolerate haplo-identical bone marrow transplant without rejection at 6 months of age [57]. IFN-γ was also provided to a patient with Omenn's syndrome, which is an autosomal recessive SCID variant characterized by clonal T-cell expansions, hypereosinophilia, and severe dermatitis [58]. Treatment of Omenn's syndrome with IFN-γ resulted in normalization of eosinophils counts and an improvement in infections [59]. The investigators attributed the effect of IFN-γ to a down-regulation in IL5 and IL10 expression in vivo and improved T-cell responses as demonstrated by phytohemagglutinin-induced proliferation [59]. IFN-γ treatment has additionally been studied in two patients with ICD4L and cryptococcal meningitis [60]. Treatment resulted in resolution of meningitis, which was refractory to antifungal therapy. Finally, IFN-γ therapy has been successfully used in three unrelated groups of patients with IL-12Rβ1-deficiency infected with non-tuberculous mycobacteria (NTM) or *Salmonella* [61–63], as well as in a patient with homozygous hypomorphic partial recessive IFNγRI mutation who had refractory, disseminated mycobacteriosis [64].

Interleukin2

IL-2 therapy has been administered in eight different PID with varying degrees of success. An early use of IL-2 in PID was to treat one female patient with SCID who was deficient in IL-2 production [65] and had a defective ability to activate nuclear factor of activated T-cells [66]. Because this girl failed two bone marrow transplants, IL-2 therapy was initiated and resulted in an improvement in clinical status and T-cell proliferative responses. The patient tolerated home-based IL-2 treatment for several years and achieved normal growth parameters [67]. IL-2 has also been used in Wiskott–Aldrich syndrome, which is an X-linked recessive disease characterized by eczema, small platelets, and varying immune abnormalities due to mutations in the Wiskott–Aldrich syndrome protein gene [68, 69]. A single patient with WAS has been treated with IL-2 for intractable herpes infection and chronic eczematoid dermatitis [70]. Treatment was well tolerated and accompanied by an improvement in dermatitis and increase in CD3+ and CD4+ cell subsets [70, 71]. IL-2 was additionally used to treat a patient with a hypomorphic mutation in the gene encoding the NF-κB essential modulator (NEMO). This disease is characterized by a combined immunodeficiency with susceptibility to pyogenic bacterial and mycobacterial infections. Immunologic features include impaired proliferative responses, specific antibody production, and NK cell function [72]. Intravenous as well as subcutaneous IL-2 therapy was well tolerated over a 6-month period in the one patient with NEMO deficiency who was treated. This resulted in an improved in NK cell cytotoxicity without noted AE ([73] and unpublished results).

IL-2 therapy has been provided to patients with CVID and was well tolerated in four studies. Each utilized a specific regimen. CVID is characterized by hypogammaglobulinemia with poor antigen-specific antibody responses [74]. In 15 subjects, 12–18 months of IL-2 therapy with CVID was reported to decrease the number of days of bronchitis, diarrhea, or joint pain [75]. A double-blind placebo crossover study of IL-2 therapy in ten subjects with CVID identified reduced susceptibility of severe infections in the 6 months following treatment [76]. Intravenous administration of IL-2 conjugated to PEG was studied in five CVID patients and was found to result in a decrease in infections as well as antibiotic requirements [77]. Liposomal preparations of IL-2 were also studied in CVID, but treatment did not result in any changes in chest X-ray or pulmonary function [78]. Collectively, these studies of IL-2 in CVID reported variable effects upon lymphocyte proliferation and antibody responses.

A single patient with combined immunodeficiency (labeled as Nezelof's syndrome) was treated with IL-2 because he was found to have absence of endogenous IL-2 production [79]. Treatment was associated with an improvement in T-cell-mediated cytotoxicity. This patient, however, may have had HIV infection given the year in which the study was performed, although it was not confirmed by laboratory testing. The patient died due to pulmonary aspergillosis despite IL-2 therapy [79]. IL-2, however, has been reported to have measurable benefits in HIV-infected individuals [80].

IL-2 has been utilized in ataxia telangiectasia (AT), which is caused by a mutation in the ATM gene and is characterized by early onset cerebellar ataxia, telangiectasias, hypogammaglobulinemia, and increased incidence of malignancies [81]. A patient with AT demonstrated to have a lack of IL-2 production was treated with IL-2 in an effort to ameliorate pneumonia [82]. Therapy resulted in an

improvement in clinical status, response to T-cell mitogens and serum IgM but did not increase IgG levels. IL-2 administration has also been anecdotally evaluated in the 22q11.2 deletion syndrome, which is associated with developmental defects, variable thymic insufficiency, defects in T-cell immunity, and an increased incidence of infection and autoimmune disease [83]. IL-2 treatment has been administered to one subject with 22q11.2 deletion syndrome and was reported to increase T-cell counts. Proliferative responses to mitogens, however, remained depressed. The subject died of respiratory failure despite IL-2 treatment [84].

Finally, IL-2 therapy has been administered in two separate patients with ICD4L. In the first study patient, there was a treatment-associated improvement in preexisting mycobacterial disease, CD4+ T-cell counts, B-cell counts, and T-cell proliferation [85]. In a second patient who had cryptococcal meningitis, 1-month of IL-2 therapy resulted in resolution of meningitis and an increase in CD4+ T-cell count [86].

Combination cytokine therapy

In two studies, more than one type of cytokine therapy (G-CSF and GM-CSF combinations excluded) was administered to individuals with PID. A patient with cyclic neutropenia had resistant generalized verrucosis (HPV) for 13 years and was treated with IFN-γ and GM-CSF, After 6 months of therapy, HPV DNA was undetectable in skin samples of regressed warts, indicating that HPV latency had been abolished [87]. A patient with CVID and an abnormal CD8+ T-cell subset was treated with IL-2 and IFN-γ in an effort to improve preexisting progressive multifocal leukoencephalopathy (PML) due to JC virus. IL-2, however, was withdrawn due to the development of a presumably related widespread psoriaform rash. The patient's condition ultimately deteriorated leading to death [88].

Summary

Despite having been studied in PID for over 20 years, cytokine therapies have a very limited role in the treatment of these diseases. The best substantiated uses of cytokine therapy in PID are that of G-CSF for congenital neutropenia and IFN-γ in CGD. Both of these uses carry an FDA-approved indication. The CGD application, however, was considered before the widespread availability of modern antifungal prophylaxis, and thus, its current routine use in this disease is variable. Given their specific ability to stimulate immunity, cytokine therapies hold great promise in individuals with defective immunity. Several obstacles, however, have likely affected the broader study and clinical application of these molecules. These include the significant costs associated with studies of biological therapies as well as the fine balance between therapeutic and adverse effect. During normal immune responses, cytokines are very tightly regulated, and thus, it is likely that very specific pharmacokinetics will be required to elicit beneficial responses. Identifying these requires complex studies, which may prove burdensome. Continued efforts in this field however will likely unlock additional valuable therapeutic potential of cytokines in PID.

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