

Variable Clinical expressivity of STAT3 Mutation in Hyperimmunoglobulin E Syndrome: Genetic and Clinical Studies of Six Patients

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Abstract

Background and purpose Autosomal dominant Hyper IgE syndrome (AD-HIES) is a rare and complex primary immunodeficiency that affects multiple systems. Mutations in signal transducer and activator of transcription 3 (*STAT3*) gene cause AD-HIES. These mutations have a dominant-negative effect

and the presence of such mutations is associated with a clinical phenotype. We aim to describe genetic and clinical characteristics of patients with AD-HIES in our clinic and to highlight the variability of clinical patterns in the same family.

Methods We describe six patients, four individuals of the same family and two unrelated patients. All patients were given a clinical score based on disease phenotype according to the National Institute of Health (NIH) score. Mutation analysis of *STAT3* was done by PCR amplification of all coding exons followed by bidirectional sequencing using the BigDye kit v1.1 and an ABI3700 genetic analyzer (Applied Biosystems).

Results All six patients had DNA binding region point mutations: a proband and his three children with p.Phe384Leu mutation, a patient with p.Arg382Trp substitution and a patient with p.Arg382Gln mutation. All of these mutations were previously reported. Patients differed in infectious, immunologic and somatic features. We observed an extreme variability in disease phenotype within the reported family with one genetically affected patient displaying an ‘unaffected’ phenotype.

Conclusions Although the genetic cause of AD-HIES is known, more studies are required to better understand the possible additional factors that may affect disease expressivity within families and the clinical diversity of the disease.

Keywords Autosomal dominant Hyperimmunoglobulin E Syndrome · *STAT3* mutations · Clinical expressivity

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Introduction

Autosomal dominant Hyper IgE syndrome (AD-HIES) is a rare and complex primary immunodeficiency that affects

multiple systems. It is characterized by elevated IgE, recurrent skin and pulmonary infections and eczematoid dermatitis. Somatic manifestations include scoliosis, joint hyperextensibility, impaired shedding of deciduous teeth and facial dysmorphism [1–3].

Recently, various mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene were identified in patients with AD-HIES pointing to the molecular basis of this disease [4]. The Janus Kinase (*JAK*)-*STAT3* pathway is involved in the signaling and control of various families of cytokines and consequently has a major role in immunologic pathways. Indeed, combined immunologic defects were largely reported in these patients [5].

Mutations in *STAT3* gene in patients with AD-HIES have a dominant-negative effect and are usually located in the DNA-binding domain or the Src homology 2 (SH2) domain of the gene [5]. Patients with *STAT3* dominant-negative mutations usually demonstrate the clinical phenotype of AD-HIES [1]. Although past studies failed to show clinical differences between patients bearing different mutations, considerable phenotypic variation within families was reported [6,7]. This suggests possible involvement of additional environmental, genetic and epigenetic factors in the pathogenesis and clinical expression of the disease.

To date, management of this disease is largely supportive and consists of preventing infection by using anti-microbial and/or anti-fungal prophylaxis and giving aggressive treatment for acute infections. Many efforts are devoted to treat the sequel of disease, such as chronic lung disease and skeletal deformations. Immunomodulatory agents have been tried with limited success [1].

In this report we describe six patients, four individuals of the same family and two unrelated patients, all having a mutation in *STAT3* that is consistent with AD-HIES. The family includes a proband and three children with variable clinical expression. The other 2 patients received an unusual treatment with cyclosporine A (CSA). This intervention resulted in a very good effect on the clinical course of the disease with a parallel normalization of neutrophil chemotaxis as well as gradual decreased of IgE levels [8]. We here report the genetic studies and the long term outcome of these patients.

Methods

Patients

All patients were followed at the Pediatric Hemato-Immunology clinic at the Meir Medical Center and at the immunology clinic at Schneider Children's hospital at Rabin Medical Center. The phagocytic studies were performed at the National Laboratory of Leukocyte Functions of the Meir Medical Center at Kfar Saba. All demographic, laboratory

and clinical data were extracted from patient's charts. All patients were given a clinical score based on disease phenotype according to the scoring system previously reported by the National Institute of Health (NIH) [9].

The study was approved by the Institutional Review Board of Meir Medical Center and conducted in accordance with the ethical and humane principles of research established by the Helsinki Declaration.

Genetic studies

Mutation analysis of *STAT3* was done by PCR amplification of all coding exons followed by bidirectional sequencing using the BigDye kit v1.1 (Applied Biosystems) and an ABI3700 genetic analyzer (Applied Biosystems). Sequence results were analyzed using CodonCode aligner (CodonCode Corporation). Primer sequences and PCR conditions are available on request.

Results

Over two decades we have encountered several patients with recurrent microbial and fungal infections who were clinically diagnosed with the Hyper-IgE syndrome (HIES). The summary of these patients' clinical features and genetic studies are shown in Table 1 and Figs. 1 and 2. The immunologic data of the patients are reported in Table 2.

Patient 1 (P1) is a male who presented with a neonatal rash. At the age of 2 months he developed sepsis. His IgE levels were high (21,200 IU/ml) as was his absolute eosinophil count (AEC). He suffered from dermatitis with secondary superimposed infections (Fig. 2), recurrent pneumonias, acute suppurative otitis media, suppurative lymphadenitis, esophageal candidiasis and abscesses in various locations (skin, perianal, liver, kidney and ocular abscess). At the age of 13 years he suffered from cryptococcal meningitis requiring the introduction of a ventriculo-peritoneal shunt and prolonged treatment with fluconazole. Two years later he had pulmonary aspergilloma that was treated with the combination of surgery and itraconazole. At the age of 17 years he developed an infection of the shunt that required replacement. Somatic features included characteristic facial changes, scoliosis ($>20^\circ$), hyper-extensibility of the joints and impaired shedding of deciduous teeth. Chronic sequelae related to recurrent infections included chronic lung disease, right pneumothorax with broncho-pleural fistula and the formation of left upper lobe bulla (pneumatocele). Other chronic complications included hearing impairment, arterial hypertension and impaired cholestatic liver functions. His NIH score was 92. The genetic analysis of *STAT3* demonstrated a point mutation at the DNA binding region with the amino acid substitution of phenylalanine to leucine at position 384 (p.Phe384Leu; c.1152 T>G).

Table 1 Demographic, clinical and genetic characteristics of patients

	Patient #1 Father	Patient #2 offspring	Patient #3 offspring	Patient #4 offspring	Patient #5	Patient #6
Sex	Male	Male	Female	Male	Male	Male
Age at data collection (years)	33	9	8	6	33	20
STAT3 mutation/domain	F384L/ DNA binding domain	F384L/ DNA binding domain	F384L/ DNA binding domain	F384L/ DNA binding domain	R382W/ DNA binding domain	R382Q/ DNA binding domain
NIH score [1]	92	60	12	30	54	94
IgE (highest; IU/ml)	21200	19500	61	529	60000	19600
Eosinophil count (highest; AEC×10 ³ /μL)	1100	2700	700	12,000	550	810
Chemotactic defect	Variable	Absent	Absent	Absent	Present	Present
Eczema – worst stage	Moderate	Severe	Absent	Mild	(43 % of control)	(4 % of control)
Parenchymal lung anomalies	Rt. Pneumothorax, Rt. Broncho-pleural fistula LUL bullae	Pneumatocele+pleural effusion	Absent	Atelectasis	Moderate Pneumatocele	Severe Bilateral severe bronchiectasis
Infectious manifestations						
Skin abscess (episodes per lifetime)	>4	1	0	0	>4	>4
Pneumonia (episodes per lifetime)	>3	6	2	4	>3	>10
Candidiasis (oral/fingernails/systemic)	Esophageal Onychomycosis	Esophageal Cheilosis	Cheilosis	Oral Cheilosis	Fingernails	Fingernails
Upper respiratory infections per year	>6	3	>6	1–2	>6	>6
Other serious infections	Recurrent and fatal Cryptococcal meningitis Lung Aspergilloma	none	none	PJP infection	Inguinal/cervical/axillary lymphadenitis Suppurative otitis media	Pulmonary abscess Cervical lymphadenitis Suppurative otitis media Fatal pneumonia and sepsis
Somatic manifestations						
Scoliosis maximum curvature	Present > 20°	NA ^a	NA ^a	NA ^a	Absent <10°	Present >20°
Fractures with minor trauma	Present	Present	Absent	Absent	Absent	Present
Characteristic face	2 episodes	2 episodes			Severe osteoporosis	1 episode
Midline anomaly	Present	Present	Absent	Absent	Absent	Present
Hyper-extensibility	Absent	Absent	Absent	Absent	Absent	Absent
Increased nasal width	Present	Present	Absent	Absent	Absent	Present
High palate	Present (1–2 SD of normal)	Present (1–2 SD of normal)	Absent	Absent	Absent	Present (>2 SD)

Table 1 (continued)

	Patient #1 Father	Patient #2 offspring	Patient #3 offspring	Patient #4 offspring	Patient #5	Patient #6
Impaired shedding of deciduous teeth (Number of teeth)	Present (>3)	NA ^a	NA ^a	NA ^a	Present (10)	Present (4)
Newborn rash	Present	Present	Absent	NA	Absent	Present
Lymphoma	Absent	Absent	Absent	Absent	Absent	Absent
Outcome	Dead	Alive	Alive	Alive	Alive	Dead

NA not available, NIH National Cancer Institute, AEC absolute eosinophil count, *PJP Pneumocystis Jirovecii* pneumonia

^a Scoliosis and Impaired shedding of deciduous teeth were absent at the time of data collection but these manifestations could appear at a later age

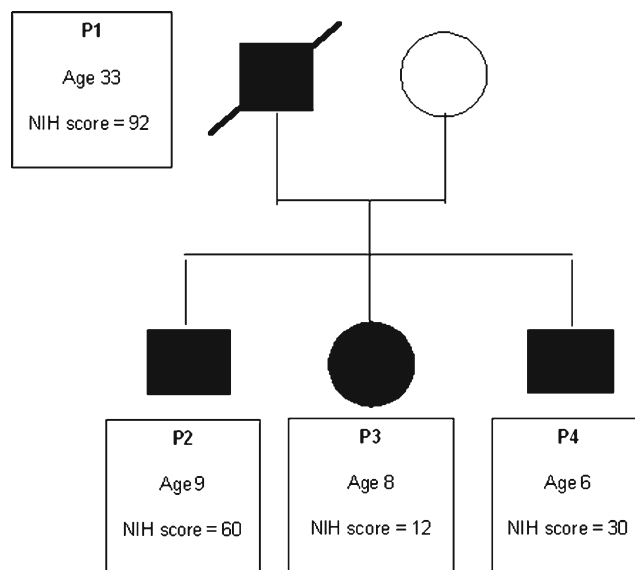


Fig. 1 Pedigree of the family reported (patients 1–4). Of note is the different phenotypic expression associated with similar genotype

At the age of 33 he was admitted to the hospital with high fever and vomiting. He was diagnosed as having recurrent cryptococcal meningitis, 20 years after the first episode. His ventriculo-peritoneal shunt was urgently removed and anti-fungal agent was started, but his clinical condition rapidly deteriorated and he died within 7 days of admission.

Patients 2, 3 and 4, offsprings of P1 (Fig. 1) were examined and found to have the same point mutation as their father. Of note, the mother of these patients tested negative for this mutation. Patients 2 (P2) and 4 (P4) bare a clinical phenotype of the disease with NIH scores of 60 and 30, respectively. P2, a 9-year old male, presented with a newborn rash and developed pneumonia at the age of 6 months. He had significantly elevated IgE levels (19,500 IU/ml) and persistently increased AEC (800 to 2700 cells/uL). He suffered from severe eczema, esophageal candidiasis and recurrent pneumonia that eventually resulted in parenchymal lung disease (pneumatocele and bilateral bronchiectasis).

P4, a 6-year old male presented at the age of 4 months with *Pneumocystis jirovecii* pneumonia (PJP). He had elevated IgE levels (529 IU/ml) and a high AEC of 12,000 cells/uL. He suffered from mild eczema, oral candidiasis and recurrent pneumonia. This patient was previously reported [10].

Despite having the same mutation as the father and both of her brothers, patient 3 (P3) did not demonstrate the AD-HIES phenotype. She was 8 years of age at data collection, having normal IgE levels (61 IU/ml) and a marginally elevated AEC (700 cells/uL). She had suffered from pneumonia, recurrent URTI and frequent episodes of acute otitis media. Typical somatic features were absent. Her calculated NIH score of 12 was consistent with an ‘unaffected’ phenotype.

Patient 5 (P5) is a 33-year old male. He presented at the age of 2 weeks with an infection following circumcision. Later on

Fig. 2 Clinical spectrum of AD-HIES. Panels **a** to **d** show somatic features of the face and dermatitis with secondary superimposed infections in patient 1. Panel **e** shows severe onychomycosis in p6



he developed recurrent pneumonias with lung abscesses and pneumatocele formation, followed by a chronic lung disease that required chronic oxygen administration and prolonged antibiotic therapy. He also suffered from skin abscesses, chronic suppurative otitis media and various episodes of

suppurative inguinal, cervical and axillary lymphadenitis. The most striking somatic feature in this patient was impaired shedding of deciduous teeth (10 teeth) that required surgical intervention. He had an extremely high IgE level (60,000 IU/ml) and a mildly elevated AEC (550 cells/uL). His NIH score

Table 2 Immunologic characteristics of patients

	Patient #1 Father	Patient #2 offspring	Patient #3 offspring	Patient #4 offspring	Patient #5	Patient #6
AEC $\times 10^3/\mu\text{L}$ ($N < 500$)	1.1	2.7	0.7	12	0.55	0.81
IgG (mg/dL; $N 923 \pm 256$)	1680	1540	1490	1590	1330	1070
IgM (mg/dL; $N 65 \pm 25$)	194	113	105	304	192	118
IgA (mg/dL; $N 124 \pm 45$)	169	86	85	32	171	121
IgE (IU/mL; $N < 150$)	21200	19500	61	529	60000	19600
C3 (mg/dL; $N 80\text{--}140$)	100	140	127	NA	185	130
C4 (mg/dL; $N 10\text{--}30$)	30	23	18	NA	24	39
CH50	Normal	Normal	Normal	NA	Normal	Normal
CD3 (%)	73	77	82	80	76	74
CD4 (%)	48	47	45	53	39.5	33
CD8 (%)	24	25	31	20	34	36
CD4/CD8	2	1.9	1.5	2.7	1.1	0.9
CD19 (%)	7	20.5	10.4	17.4	19	18.5
CD20 (%)	7	20.3	10.3	17.2	NA	18
CD56+/CD3- (%)	1	1	4	3	1.4	1.5
Skin test (PPD/Candida)	Negative	NA	NA	NA	Negative	Negative
DPT-Sabin Ab	Negative	NA	NA	NA	Negative	Low
Neutrophil chemotaxis	↓	Normal	Normal	Normal	↓	↓

N normal range, *AEC* absolute eosinophil count, *NA* not available

was 54. Genetic analysis of *STAT3* demonstrated a point mutation at the DNA-binding region with amino acid substitution of arginine with tryptophan at position 382 (p.Arg382Trp; c.1144C>T).

Patient 6 (P6) is a 20-year old male at data collection. He presented with a skin rash at birth and suffered from recurrent pneumonia, chronic suppurative otitis media and severe eczema. He also developed suppurative cervical lymphadenitis and a lung abscess. The recurrent pulmonary infections resulted in severe bilateral bronchiectasis. Somatic features associated with AD-HIES were pronounced in this patient and included a characteristic face, high palate, severe scoliosis (>20°), hypermobility of the joints, impaired shedding of deciduous teeth (4 teeth) and a wrist fracture following a minor trauma. Of note was the chronic severe onychomycosis (Fig. 2). He had high IgE levels (19,600 IU/ml) and an elevated AEC (810 cells/uL). P6 died at the age of 20 years of pneumonia complicated by sepsis. His NIH score was 94. Genetic analysis of *STAT3* demonstrated a point mutation at the DNA-binding region with amino acid substitution of arginine at position 382 in the protein with a glutamine residue (p.Arg382Gln; c.1145G>A).

In patients reported herein *Staphylococcal spp.* were the most common bacteria recovered from skin and deep-seated abscesses, in the perianal region, liver and kidneys. Gram-negative bacteria, as *Proteus spp.* and *E. coli spp.* were recovered in urine cultures in two patients and *Pseudomonas aeruginosa* was recovered from the ears of three patients (P1, P5, P6). *Candida albicans* was isolated from the skin and mucous membranes in four patients (P1, P2, P5 and P6). *Cryptococcus spp.* was recovered from the CSF in one patient (P1), *Aspergillus fumigatus* from the lung of P5 and *Pneumocystis jirovecii* isolated from the lung of P4. Standard anti-staphylococcal prophylaxis with amoxicillin-clavulanate or cephalosporins was administered to all patients who developed a major infection. Anti-mycotic prophylaxis was initiated in patients who suffered from protracted mycotic infections. Itraconazole or fluconazole were administered for candidiasis while voriconazole or itraconazole was given for infections with aspergillus spp.

Discussion

In 1966 Davis et al. reported on two unrelated females with Job's syndrome [11]. It was only 4 decades later that Minegishi et al. and Holland et al. published their pivotal studies describing heterozygous mutations in the *STAT3* gene among patients with the HIES clinical phenotype [4,12]. Genetic analysis of one of the original patients described by Davis et al. was performed and demonstrated a point mutation in the *STAT3* gene (c.1144C>T; p.Arg382Trp)[13].

The clinical phenotype of AD-HIES was previously described as one of both excessive and inadequate inflammation [1]. The discovery of *STAT3* mutations as the cause of AD-

HIES explains much of the clinical, laboratory and immunologic findings in this syndrome. The *JAK-STAT* pathway is involved in regulation and expression of various cytokines. These include both pro-inflammatory and anti-inflammatory cytokines such as IL-6, IL-10, IL-21, IL-22 and IL-23[1]. Perturbations in the level of different cytokines and in the number and function of specific lymphocyte subpopulations were observed in *STAT3* knockout mice models as well as in human studies. Elevated levels of TNF-alpha and IFN-gamma were demonstrated in *STAT3* knockout mice [14]. B-memory cell lymphopenia was demonstrated in patients with AD-HIES as was a near total absence of Th17 cells [6]. The latter finding is associated with severely impaired IL-17 and IL-22 secretion, that are both linked to the susceptibility to skin and mucosal recurrence of staphylococcal and candida infections [1]. The cause for the strongly elevated IgE levels is still not clear, although the role of reduced IL-21 has been suggested to contribute to the IgE isotype switch [15].

Past studies demonstrated that the majority of *STAT3* mutations are localized to the DNA-binding region and the SH2 domain. In these domains mutational hotspots were reported. Rare mutations in the transactivation and coiled-coil domain were reported as well [4,6].

In our study we describe six patients bearing DNA binding region point mutations: a proband and his three children (P1 to P4) with the p.Phe384Leu mutation, patient 5 with the p.Arg382Trp substitution and patient 6 with the p.Arg382Gln mutation. All of these mutations were previously reported. The two latter mutations (p.Arg382Trp and p.Arg382Gln) are located at mutational hotspots [4,6,7].

A major finding in our study is the extreme variability in clinical expression of the mutation within the reported family. P1 and two of the genetically affected offspring (P2 and P4) demonstrated a clinical phenotype consistent with AD-HIES in accordance to the NIH score. Sibling P3 although carrying the same *STAT3* mutation did not have a clinical phenotype reminiscent of AD-HIES (NIH score of 12). Variations in the phenotypic presentation within families were previously reported [4,6,7].

The clinical phenotype of patients with AD-HIES is commonly characterized by the NIH score first introduced by Grimbacher and colleagues [9]. In the pivotal study by Holland and colleagues [4] NIH scores were arbitrarily categorized to define patients as 'unaffected' (score of 0–15), 'possibly affected' (score of 16–39), 'probably affected' (score of 40–59) and 'definitely affected' (score above 60). Woellner and colleagues studied the NIH score ability to predict *STAT3* mutations in patients with suspected HIES. NIH score of 49.5 was found to be the optimal cutoff for predicting a *STAT3* mutation with a very high sensitivity (97 %) but a rather low selectivity (58.8 %) [3].

In this study 3 patients (P1, P2 and P6) were 'definitely affected', one was 'probably affected' (P5), one was 'possibly

affected' (P4) and one 'unaffected' (P3). In their study Holland and colleagues reported a good correlation between NIH score and genotype with all but one of the 50 genetically affected patients [4]. Few patients had a score compatible with 'possibly affected'. Chandesris and colleagues [6] reported on 60 additional patients with autosomal-dominant *STAT3* deficiency in France. Of these patients two had NIH scores that would be considered to have the 'unaffected' phenotype. The first subject is an 11-year old female with a mutation resulting in the p.Val463del change and the second subject is a 7-year old male with the p.Phe384Leu mutation. Both patients had an NIH score of 14. There are some interesting similarities between these subjects and P3 in our study that has an NIH score of 12. All three subjects have DNA-binding domain mutations and are young at diagnosis. Moreover, in all cases siblings and the affected parent have NIH scores that are significantly higher and would be considered 'possibly', 'probably' or 'definitely affected'. Note that P3 and the 7-year old male in the cited study share the same predicted p.Phe384Leu amino acid change.

Heimall et al. studied 65 patients with AD-HIES of whom 35 patients had been identified with mutations in the DNA-binding domain and 30 with mutations in the SH2 domain. The overall clinical phenotype did not differ between patients with different mutations, although patients with SH2 domain mutations exhibited an increased frequency of high palate, broad inter-alar distance, scoliosis and upper respiratory infections [7]. In that study no 'unaffected' individuals were identified.

In the present study, only two affected children (P2, P4) had persistent eosinophilia. There was no correlation between the neutrophil chemotaxis function and the severity of the disease (Tables 1 and 2). This is in line with the conflicting evidence on defective chemotaxis and its implications in AD-HIES [16]. We did not assess TH17 and B memory cell compartments in our patients.

A possible explanation for the lack of a full clinical phenotype among patients carrying mutations that define AD-HIES, could be related to their young age. It may be that they have not yet expressed the full clinical phenotype. For example, the median age for diagnosis in one report from the NIH was 7 years [7]. In another report from a multicenter French study the median age at first infection was 10.5 months (range 0–180 months) [6]. However, it should be noted that the NIH score takes into account this hypothesis and points are added based on young age (up to 5 years of age).

Recently, Hsu and collaborators [17] reported on another potential explanation for phenotypic variation in disease manifestation based on the analysis of two families with AD-HIES. The probands of these families showed somatic mosaicism associated with intermediate phenotypes as compared to their affected offsprings that expressed a more severe clinical phenotype. Of note, these two patients had normal TH17 cell

compartment as well as normal B memory cell expression. Nevertheless, both subjects with somatic mosaicism had a NIH score above 40 consistent with an affected phenotype and suffered from chronic mucocutaneous candidiasis.

The most commonly used immunomodulatory treatment in patients with AD-HIES consists of the administration of intravenous immunoglobulins (IVIG). According to the French multicenter experience, 53 % of 60 patients with AD-HIES received IVIG maintenance therapy. It was reported that the use of IVIG was associated with a significant decrease in the incidence of bacterial pneumonia (27.8/100 patients with pneumonia per year in the absence of IVIG vs. 9.3/100 patients with pneumonia per year with IVIG support; $p=6 \times 10^{-6}$) [6].

In 1996 we reported on the favorable effect of CSA on the disease phenotype. Patients were treated for 18 months with 5 mg/kg/day of CSA and showed a dramatic improvement in their clinical and immunologic condition. This included marked improvement in eczema, lack of significant infections and reduced hospitalizations, along with a two-log reduction in IgE titer and a marked improvement in neutrophil chemotaxis [8]. The clinical expression of the disease and the laboratory findings promptly relapsed 1 month after the cessation of CSA. In P5 re-administration of CSA resulted once again in rapid clinical improvement. Therapy was stopped after 1 year since there was a lack of robust evidence supporting this therapy in patients with AD-HIES and because of concerns regarding long term side effects. CSA has inhibitory properties on most T cell populations. T cells treated with CSA show lower levels of IFN-gamma and TNF-alpha [18]. These cytokines are reported to be elevated in *STAT3*-deficient mice [14]. Conversely, CSA has been reported to have an inhibitory effect also on IL17-producing T cells [18]. Since IL17 is near absent in patients with AD-HIES [19], this effect of CSA is probably of limited relevance.

Although the genetic cause of AD-HIES is known, more studies are required to better understand the possible effects of environmental, immunological, genetic or epigenetic factors on the disease phenotype. More studies on novel treatment approaches, specifically immunomodulatory therapies, such as IVIG or CSA, are needed.

Conflict of Interest The Authors declare they have no conflict of interest.

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