Tocilizumab for the Treatment of SLC29A3 Mutation Positive PHID Syndrome

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Pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (PHID) is associated with recessive mutations in SLC29A3, encoding the equilibrative nucleoside transporter hENT3 expressed in mitochondria, causing PHID and H syndromes, familial Rosai-Dorfman disease, and histiocytosis-lymphadenopathy-plus syndrome. Autoinflammation is increasingly recognized in these syndromes. We previously reported a 16-year-old girl with PHID syndrome associated with severe autoinflammation that was recalcitrant to interleukin-1 and tumor necrosis factor-α blockade. Tocilizumab is a humanized, monoclonal, anti-human interleukin-6 receptor antibody routinely used to treat arthritis in children and adults. Herein we report the first case of successful treatment of PHID syndrome using tocilizumab. Before commencing tocilizumab, there was evidence of significant systemic inflammation, and progressive sclerodermatous changes (physician global assessment [PGA] 7/10). Twelve weeks after starting tocilizumab (8 mg/kg every 2 weeks, intravenously) systemic inflammatory symptoms improved, and acute phase response markers normalized; serum amyloid A reduced from 178 to 8.4 mg/L. After a dose increase to 12 mg/kg every 2 weeks her energy levels, appetite, fevers, and night sweats further improved. Less skin tightness (PGA 5/10) was documented 12 months later. This excellent clinical and serological response was sustained over 48 months, and cutaneous sclerosis had improved further (PGA 3/10). Her height remained well below the 0.4th centile, and tocilizumab also had no impact on her diabetes or exocrine pancreatic insufficiency. Although the mechanism of autoinflammation of PHID remains uncertain, we suggest that tocilizumab should be the first choice when considering treatment of the autoinflammatory or cutaneous manifestations of this genetic disease.

Dr Rafiq drafted the initial manuscript; Drs Hussain and Brogan reviewed and revised the manuscript, and all authors approved the final manuscript as submitted.

DOI: https://doi.org/10.1542/peds.2016-3148
Accepted for publication Feb 27, 2017
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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Dr Brogan has received institutional grant funding and consultancy fees from Roche; Drs Rafiq and Hussain have indicated they have no potential conflicts of interest to disclose.

which was recalcitrant to treatment with blockade of interleukin (IL)-1 and tumor necrosis factor α (TNF-α).

IL-6 is a physiologically important cytokine involved in physiologic immune responses and inflammation. Abnormal continuous production of IL-6 is associated with pathogenesis of various autoimmune disorders. Tocilizumab has been used to successful response to IL-6 blockade in this rare genetic disease. Using tocilizumab for the treatment of monogenic autoinflammatory diseases is limited. We herein describe our experience of tocilizumab for the treatment of PHID syndrome, which to the best of our knowledge is the first report of successful response to IL-6 blockade in this rare genetic disease.

**CASE REPORT**

Written informed consent was provided for the publication of this report.

A 16.5-year-old girl with PHID caused by a homozygous T449R mutation in the SLC29A3 gene was born at term to consanguineous parents of Pakistani origin. She has 3 siblings, 2 unaffected and a 22-year-old female sibling who also has PHID syndrome caused by the same homozygous mutation. The full clinical course and detailed investigations have previously been reported by our group. In summary, she first presented with features of PHID at age 9 months with hyperpigmentation and hypertrichosis affecting her back and legs. Lesional skin biopsy revealed nonspecific inflammatory changes. Throughout her childhood and adolescence, she had poor weight gain, stunted growth, recurrent severe pyrexias and night sweats, fatigue, and chronic diarrhea. Acute phase markers were constantly elevated; erythrocyte sedimentation rate (ESR) was consistently 160 mm/hour or higher, C-reactive protein (CRP) was usually >60 mg/L, and there was significant anemia (hemoglobin 60–90 g/L). At age 4 years she developed diabetes mellitus necessitating insulin treatment. Islet cell and glutamic acid decarboxylase antibodies were negative; exocrine pancreatic insufficiency was also detected around this time, and she required pancreatic enzyme replacement therapy. The skin on her arms and legs showed increased tightening the typical sclerodermatous-like changes over the years. Biopsies from lymph nodes and subcutaneous tissue showed fibrofatty connective tissue with fibrosis and mononuclear cell infiltrates around the larger vessels. Inflammatory markers such as the ESR, CRP, and serum amyloid A (SAA) were constantly raised. She also had persistent hepatomegaly and splenomegaly. Despite evidence of systemic involvement, her cognition remained normal.

Daily prednisolone (varying from 0.2 to 1 mg/kg daily) was required for most of her early life to control systemic inflammatory features. This temporarly improved her inflammatory symptoms and ESR; upon weaning, however, her inflammatory symptoms and acute phase markers deteriorated. She was therefore treated with high-dose pulsed intravenous methylprednisolone (30 mg/kg daily for 3 days), plus subcutaneous methotrexate (15 mg/m²) in an attempt to spare the daily prednisolone dose. Nine months after commencing methotrexate, there was partial improvement in skin tightness but still significant systemic inflammation. Her blood results at this point revealed elevated SAA 178 mg/L, CRP 54 mg/L, and ESR 86 mm/hour.

At age 10 years, peripheral blood cytokine analysis, measured by enzyme-linked immunosorbent assay, was performed in an attempt to identify potential therapeutic targets. These revealed a normal IL-6 level of 4.9 pg/mL (reference range 0.43–8.9 pg/mL), and a raised TNF-α of 68 pg/mL (reference <15.6 pg/mL). IL-1β has a short half-life and usually functions in an autocrine and/or paracrine manner; hence measurement of this cytokine in peripheral blood is usually uninformative and was thus not assessed in this case. Due to persistently raised SAA measurements ranging between 99 and 127 mg/L, we gave her a trial of daily anakinra (IL-1 blockade), 50 mg (2.3 mg/kg/day subcutaneously) for a month. This had no clinical impact on her systemic inflammatory features or serological markers of inflammation; SAA remained elevated (104–164 mg/L) 4 weeks after starting, despite a dose increase to 100 mg daily. Anakinra was subsequently stopped. Because of persistent systemic inflammation, 1 year later, she started subcutaneous adalimumab (a humanized monoclonal antibody against TNF-α) 40 mg every 2 weeks. Despite this, she continued to have severe ongoing inflammatory symptoms, and raised inflammatory markers. Adalimumab was therefore discontinued 4 months later.

At age 12, she reported exertional dyspnoea; cardiac MRI revealed hypertrophic cardiomyopathy, which is not typical of cardiac amyloidosis, as previously reported. Clinical deterioration in the context of severe ongoing systemic...
inflammation that was recalcitrant to methotrexate, anakinra, and adalimumab necessitated consideration of empirical treatment with tocilizumab, despite normal circulating levels of IL-6. To assess her clinical response to this treatment, we evaluated improvement based on patient-reported improvement in fever episodes and night sweats; energy levels; growth; clinical response of the sclerotic skin changes using physician global assessment (PGA) of severity on a 10-point scale (0 indicating no sclerotic skin disease, 10 signifying severe sclerotic skin disease); and change in acute phase markers (CRP, ESR, and SAA). Change in hypertrichosis was not possible to evaluate because the patient regularly removed the hair from cutaneous lesions. Intravenous tocilizumab was started at 8 mg/kg, every 2 weeks, initially combined with methotrexate (15 mg/m² per week) and prednisolone (0.4 mg/kg/day). At 12 weeks of treatment her inflammatory markers improved significantly: CRP <5 mg/L, ESR 22 mm/hour, and SAA 8.4 mg/L, although PGA of the skin remained 7/10. Her dose was therefore increased to 12 mg/kg every 2 weeks. Almost immediately she reported marked clinical improvement in her energy levels, improved appetite, much improved fevers and night sweats (from >5 episodes per week to ~1 per week), and subjectively less skin tightness. Prednisolone was gradually weaned, and the methotrexate was discontinued 9 months after commencing tocilizumab due to continued excellent clinical and serological response. Ten infections occurred after treatment with tocilizumab. These were mostly respiratory tract infections of presumed viral cause, 4 being defined as serious requiring hospital admission and empirical intravenous antibiotics. The only positive microbiology for these infections was a positive urine for Escherichia coli on 1 occasion. There were no other reported adverse events.

The serological and cutaneous response to tocilizumab and episodes of infection are summarized in Fig. 1. At final follow-up aged 16.5 years, height (131.7 cm) and weight (35.9 kg) remained well below the 0.4th centile despite the fact she has also been commenced on growth hormone treatment. She remains under cardiac review, and although she continues to have biventricular hypertrophy, her global systolic function is currently preserved.

**DISCUSSION**

PHID syndrome has an important autoinflammatory component that is increasingly recognized in the
context of the other cardinal features of the disease, namely pigmentary hypertrichosis (usually with sclerodermatous changes) and both endocrine and exocrine pancreatic insufficiency. Virtually nothing is known about the mechanism of autoinflammation in PHID and related diseases caused by mutation in SLC29A3. One study showed that the inflammatory response involves activation of NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells), a major transcription factor responsible for the regulation of cytokine production, suggesting that there could be increased production of TNF-α and other major pro-inflammatory cytokines.9

In support of this, we documented significant elevation of serum TNF-α, but not IL-6. Alternatively, nucleoside accumulation secondary to loss of function of hENT3 nucleoside transport activity in macrophages could contribute to excess cytokine production and immune activation.9–11 In support of this, Hsu et al12 demonstrated altered macrophage function in a murine model of PHID, the ENT3 knockout mouse. ENT3 is an essential transmembrane transporter maintaining lysosomal integrity by regulating nucleoside trafficking. ENT3 deficiency, through defects in the lysosomal system, caused ineffective apoptotic cell clearance and increased macrophage colony-stimulating factor signaling that contributed to elevated numbers of macrophages and histiocytosis. These findings could provide an important cellular and molecular mechanism for the histiocytosis and autoinflammation seen in humans with PHID syndrome and might predict that blockade of IL-1 and TNF-α would be ineffective, as in our case, and another case recently described.13

We report the first case of PHID syndrome treated with IL-6 blockade, with successful outcome in relation to systemic inflammation, cutaneous skin lesions, and overall quality of life, which has so far been sustained over 48 months. Linear growth, diabetes, and exocrine pancreatic insufficiency did not improve, however. Despite relatively mild infectious adverse events that we have documented (which are well known to be associated with tocilizumab in children and adults), the overall improvement in quality of life has been dramatic for this patient. Although the mechanism of autoinflammation of PHID syndrome remains uncertain, this case highlights an important role for IL-6 in the pathogenesis of autoinflammation associated with recessive mutations in SLC29A3. Our case also highlights yet again that peripheral blood cytokines are poor biomarkers on which to base predictions regarding efficacy for empirical treatments.14 We suggest that tocilizumab should be the first choice when considering treatment of the autoinflammatory component of this extremely rare genetic disease. At the time of writing, her similarly affected sister is now also commencing tocilizumab.

ABBREVIATIONS

CRP: C-reactive protein
ESR: erythrocyte sedimentation rate
IL: interleukin
IL-6R: interleukin-6 receptor
PGA: physician global assessment
PHID: pigmented hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus
SAA: serum amyloid A
TNF-α: tumor necrosis factor α

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DOI: 10.1542/peds.2016-3148 originally published online October 27, 2017;

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