CASE REPORT

Anti-interleukin 6 receptor therapy for hyper-IgD syndrome

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SUMMARY

Hyper-IgD syndrome (HIDS) is a rare, severe hereditary autoinflammatory disease characterised by periodic fevers, elevated serum IgD levels and a wide range of symptoms. Although a few randomised controlled trials have been performed in this disorder, there are no straightforward treatment protocols and none of the potential therapies are registered for this indication. We report a case of a young woman with severe HIDS who failed numerous therapies. Eventually, rational treatment with a monoclonal anti-interleukin 6 receptor antibody was initiated. This therapy resulted in an impressive clinical improvement and reduction in the number of hospital admissions per year. This case report underlines the difficulty of finding a suitable treatment for rare, severe inflammatory diseases. Furthermore, we show that treating patients with targeted therapies may result in clinical benefit for the patient, as well as simultaneously teach us more about the pathophysiology of these rare, relatively understudied diseases.

BACKGROUND

Patients with rare, severe, therapy-refractory immune-mediated inflammatory diseases (IMIDs), are particularly difficult to treat, since treatment protocols are mostly lacking and randomised controlled trials are often impossible to conduct. Therefore, these patients are increasingly treated off-label with targeted therapies after failing on standard therapies. Off-label prescription may give early access to new valuable treatments for patients and teach us more about the pathophysiology of the disease. Consequently, off-label treatment adds to the innovation of clinical practice.

Our manuscript highlights the difficulty of finding the optimal treatment for patients with rare, severe IMIDs who are refractory to 'standard' therapies. We illustrate this using a case of a young woman with hyper-IgD syndrome (HIDS), a rare, hereditary auto-inflammatory disease. After failing on several treatment strategies, rational anti-interleukin 6 receptor therapy was initiated off-label, based on pathophysiological indications that this cytokine may play an important role in the disease. This resulted in remarkable clinical improvement with a substantial reduction in the number of hospital admissions per year. Besides this discovery of a potential valuable therapy for patients with HIDS, this case and the 'reverse immunology' approach may also teach us more about the pathophysiology of this disease.

CASE PRESENTATION

A 36-year-old woman was diagnosed with HIDS in 2002, when she was 23 years of age. The diagnosis

was based on episodic fever since childhood accompanied by abdominal pain, lymphadenopathy and hepatosplenomegaly. In addition, she had many recurring otorhinolaryngeal infections, for which she was treated with tympanostomy tubes and adenotomy. At the time of diagnosis, her serum IgD level was 750 kU/L (upper limit 120 kU/L). This was accompanied by a relatively low mevalonate excretion in urine (urine mevalonic acid/creatinine ratio of 3.0 mmol/mol) creatinine. Mevalonate excretion in urine is usually slightly elevated during a HIDS attack, but this sample was not taken during an attack. Nevertheless, the mevalonate kinase (MK) activity was 0 pmol/min/mg. Therefore these results were interpreted as consistent with MK deficiency. DNA analysis revealed heterozygosity for 417insC and the frequently found a v3771 mutation. These combined features led to the final diagnosis of HIDS and periodic fever syndrome.

In the first years after diagnosis, due to a poor social network, almost every attack this patient experienced resulted in hospital admission (on average 11 times per year) to optimise management of unbearable pain, mostly in the abdominal region, in combination with severe lymphadenopathy and fever. During these attacks, C reactive protein (CRP) levels typically spiked to 200 mg/L and higher.

TREATMENT

Initially, our patient was treated with non-steroidal anti-inflammatory drugs (NSAIDs), but later, simvastatin 40 mg daily was added in the setting of a clinical trial. The simvastatin dose was eventually increased to 80 mg daily. Despite the fact that five of the six patients in this trial had a decrease in the number of febrile days, neither of the dosages had a clinical effect on our patient.¹

Subsequently, she only used NSAIDs, and took no other medication (as per patient's request).

However, after a substantial increase in disease activity and worsening symptoms, our patient was treated with IL-1-receptor antagonist therapy (anakinra, dose 100 mg two times a day) in April 2007.^{2–5} Initially, this was prescribed continuously, but due to patient reluctance this was changed to 'on demand'. Although this initially resulted in subjective relief of signs and symptoms, ultimately this therapy was no longer effective.

Therefore, in December 2010, off-label treatment was started with a monoclonal anti-IL-6-receptor antibody (tocilizumab, 8 mg/kg every 4 weeks). Owing to the experimental

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Figure 1 Overview of the number of hospital admissions (NSAIDs, non-steroidal anti-inflammatory drugs).

character of this therapy and the moderate beneficial effects of glucocorticoids in HIDS, tocilizumab was initially given in combination with 100 mg methylprednisolone.⁶ Eventually, the methylprednisolone was tapered and tocilizumab was given as monotherapy. Tocilizumab is registered for and mainly prescribed in patients with rheumatoid arthritis and juvenile idiopathic arthritis.

OUTCOME AND FOLLOW-UP

In our patient, tocilizumab treatment resulted in remarkable clinical improvement, illustrated by a decrease in febrile episodes and abdominal pains, and almost complete resolution of lymphadenopathy, assessed by abdominal and thoracic CT scanning. CRP levels also dropped significantly, which is a well-known effect of tocilizumab treatment in general and therefore cannot necessarily be used as a marker of disease activity. Instead, we used the number of hospital admissions as an indication of disease activity to illustrate the beneficial effect of IL-6 receptor blockade in our patient (see figure 1). After the start of tocilizumab, the number of admissions dropped from an average of 11 admissions per year to approximately 3 admissions per year. Furthermore, we observed a clear drop in serum IgD levels, from 745 to 128 kU/L.

DISCUSSION

HIDS, also known as MK deficiency, is a hereditary autoinflammatory disorder characterised by high-spiking periodic fever combined with a variety of symptoms, including abdominal pain, arthralgia, skin rash and lymphadenopathy, as well as elevated serum IgD levels.⁷ It is caused by deleterious mutations in the *MVK* gene, encoding the enzyme MK that follows 3'-hydroxy-3'-methylglutaryl coenzyme A (HMG-CoA) reductase in the isoprenoid pathway. HMG-CoA reductase can be inhibited by statins, hence the clinical trial investigating the effects of simvastatin in HIDS.¹⁸

The pathophysiology of HIDS is still largely unknown. For instance, it remains unclear what the exact role of plasma cells is in HIDS, why these plasma cells are IgD specific and how an enzyme of the cholesterol biosynthetic pathway such as MK influences IgD+ plasma cells.⁹ Serum IgD levels are not related to severity of disease, nor does the IgD concentration increase further during inflammatory episodes. However, these episodes are accompanied by increased plasma concentrations of acute phase proteins, such as CRP. In patients with active and inactive disease, inflammation-associated cytokines, particularly IL-1, IL-6 and tumour necrosis factor, are found to be elevated and peripheral blood mononuclear cells of these patients are able to

respond to stimulation with a further increase in cytokine production and increased acute phase protein-inducing capacity.^{10 11} IL-6 is a strong inducer of the acute phase response, which can result in fever, anaemia and elevations in acute phase proteins, such as CRP. Furthermore, it is a crucial cytokine for plasma cell survival and may be involved in basophil differentiation.¹² Interestingly, IgD also stimulates IL-6 release by prebasophil cells, which could lead to autocrine maturation of these cells.¹³ Basophils are, besides B cells, the only leucocytes that also bind to IgD, and cross-linking of IgD on basophils stimulates the release of proinflammatory cytokines, including IL-6, and antimicrobial mediators. Consequently, it is thought that 'IgD-armed' basophils normally function as guards of the upper respiratory tract and prevent infections. Interestingly, both IgD class switched B cells and 'IgD-armed' basophils are more frequently present in patients with autoinflammatory syndromes, including HIDS, indicating that the IL-6/IL-6 receptor and IgD pathways may be dysregulated in HIDS.^{9 14}

It can be hypothesised that the reduction in serum IgD levels in our patient after therapy may reflect reduced numbers of IgD+ plasma cells due to IL-6 receptor blockade, which in turn may result in reduced IgD-mediated stimulation of basophils and consequently reduced serum levels of IL-6 accompanied by an impaired acute phase response resulting in improvement of clinical symptoms. However, additional studies on IgD+ plasma cells and basophils are required to further elucidate the underlying mechanisms that are responsible for the beneficial effects of tocilizumab treatment in HIDS.

This case of HIDS illustrates that treatment of rare, severe and relatively unknown diseases can be challenging. Treating patients with targeted therapies may result in a beneficial clinical effect and simultaneously helps to explain more about the pathophysiology. This particular case and 'reverse immunology' approach teaches us that the IL-6/IL-6-receptor interaction is likely to play an important role in this disease, a fact that is supported by several other studies.^{10 11 15} Although additional clinical and translational studies are required to support this hypothesis, we believe that anti-IL-6-receptor therapy may provide a new therapeutic option for patients with therapy-refractory HIDS. This is supported by recent literature in which targeting the IL-6/IL-6-receptor axis was suggested to be effective in HIDS.^{15 16} Unfortunately, randomised controlled trials are often difficult to conduct in rare diseases such as HIDS. Therefore, it is crucially important to monitor effectiveness and safety in a systematic way when rare diseases are treated (off-label) with novel therapies, for instance via unbiased data collection in registries.^{17 18}

Patient's perspective

My disease has put me through a long process of searching for the correct diagnosis and treatment. This process was accompanied by many periods of sickness and hospital admissions. On earlier treatments, a secondary non-response occurred. But this was different for tocilizumab. Hospital admissions and hyper-IgD syndrome (HIDS) attacks are both substantially less frequent. This resulted in a significant improvement in the quality of my life. I do not expect to ever completely recover from this disease, but at least with the tocilizumab it is under control. I am glad that I could contribute to science in this way, to obtain more knowledge on HIDS and IL-6 blockade. I hope this will eventually help future patients with HIDS.

Learning points

- ▶ Interleukin 6 receptor blockade may be an effective new therapy for hyper-IgD syndrome.
- ▶ Treating patients with targeted therapies may result in a beneficial clinical effect and may simultaneously help to elucidate more about the pathophysiology ('reverse immunology').
- ▶ Off-label prescribing may give early access to new treatments, adding to innovation in clinical practice.

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