ABSTRACT

Background: Hyper-IgD and periodic fever syndrome (HIDS) is an hereditary autoinflammatory syndrome, characterised by recurrent inflammatory attacks. Treatment of HIDS is difficult, although simvastatin is beneficial and etanercept might be effective. Studying the treatment of a rare periodic syndrome is complicated by the varying frequency and severity of symptoms and low prevalence. Our aim was to develop a system of clinical observations to evaluate effectiveness of treatment-on-demand.

Methods: Seven fever episodes in three HIDS patients were monitored, with and without administration of etanercept or anakinra. We developed a clinical score, which includes 12 symptoms. In one patient, inflammatory attacks were provoked by vaccination.

Results and conclusions: At the onset of an attack, all patients reported a clinical score between 20 and 25. The score was used to quantify severity and define the end of an attack. Reproducible monitoring of inflammatory episodes was difficult, even in this pilot study. The effect of early administration of etanercept was variable. In one patient, a fever episode could be readily provoked within 12 to 24 hours by vaccination. In this patient, the IL-1ra analogue anakinra was more successful in aborting the inflammatory attack than etanercept. We propose that this vaccination model will allow evaluation of treatment-on-demand in a controlled setting.

KEYWORDS

Anakinra, etanercept, hyper-IgD syndrome, interleukin-1, periodic fever, TNF, vaccination

INTRODUCTION

The hyper-IgD and periodic fever syndrome (HIDS, MIM#260920) is an autosomal recessively inherited autoinflammatory syndrome, caused by deficient enzyme activity of mevalonate kinase, an enzyme in the isoprenoid pathway. Patients present with a long history of recurrent fever attacks, lasting three to seven days, accompanied by chills, headache, generalised lymphadenopathy, arthralgia, skin lesions, abdominal pain and diarrhoea. Laboratory analysis reveals an intense acute-phase response during fever attack; ex-vivo production of tumour necrosis factor (TNF)-α and interleukin (IL)-1β by monocytes and macrophages is significantly higher at the time of attack. An attack is usually preceded by a well-recognisable prodromal phase of malaise, headache and musculoskeletal symptoms. Sometimes, a (trivial) stimulus can be identified as a trigger of the attack, and most HIDS patients experience a severe inflammatory episode after any vaccination. In between two attacks patients are asymptomatic, although the acute-phase response may sometimes persist.

Until now, treatment of HIDS patients is largely supportive and very difficult. Various standard anti-inflammatory drugs (including colchicine, NSAIDS, steroids and thalidomide) have failed to suppress the attacks. We have already shown that simvastatin, an inhibitor of HMG-CoA reductase, can be beneficial in reducing the number of days of illness.
when taken continuously. Reports on the response to etanercept, an inhibitor of TNFα, in HIDS have been mixed: favourable in two children, uncertain in one, and no effect in another child.

Studying the effectiveness of a treatment for a rare periodic syndrome is complicated by its variability of frequency and severity of symptoms and its low prevalence. We have tried to develop a system of rigorous clinical observations to evaluate the effectiveness of treatment-on-demand.

METHODS

Three female Dutch HIDS patients gave written informed consent for participation in this study; the study was approved by the local medical ethical committee. The patients were not on any medication apart from that mentioned in the case observations. They were instructed to contact us at the first indication of a fever attack. When that happened, the patient was admitted to hospital for close monitoring, which included regular measurement of body temperature and blood sampling for C-reactive protein (CRP).

We asked the patients to complete a daily symptom score card, rating the absence or presence of 12 different symptoms and their severity on a scale from 0 to 10. These 12 symptoms were lymphadenopathy, nausea, myalgia, arthralgia, aphthous ulcers, abdominal pain, skin lesions, headache, sore throat, tiredness, diarrhoea and nasal congestion. This was used to develop a clinical scoring system to help better delineate the duration and severity of a fever episode. By adding the scores on the individual symptoms, a daily score could thus range from 0 to 120. At the height of a fever episode, patients experienced between 7 and 12 of these 12 symptoms, while the maximal documented score ranged from 45 to 88 points. Despite an anticipated variability in scores between patients and between separate attacks in the same patient, all patients reported a total score between 20 and 25 at the time of presentation at the start of a fever attack. Thus, a score of 20 or higher was taken to represent the presence of a fever attack, while the time point of the first score below 20 was taken as the end of the attack.

CASE OBSERVATIONS

Patient 1

A 35-year-old woman had experienced characteristic febrile attacks since the age of 3 months. At age 33, HIDS was finally diagnosed, confirmed by mevalonate kinase mutation analysis (table 1). During childhood, vaccinations used to trigger febrile attacks but the administration of hepatitis A immunoglobulin at the age of 34 years did not precipitate any symptoms. She was closely monitored during an attack which started with a sore throat, myalgias, fatigue, nausea and headache (figure 1A). Her body temperature was 36.6°C at presentation. Over the next few days symptoms increased and her body temperature quickly rose to 39.5°C, with a maximum CRP of 102 mg/l. The symptoms of the attack lasted four days although serum CRP concentration was still elevated at seven days (figure 1A).

The next time she was admitted at the start of a fever attack, two doses of etanercept (25 mg) were administered subcutaneously at 12 and 36 hours after presentation (figure 1B). There was no noticeable difference in her clinical symptoms as expressed in the clinical score, body temperature or decrease in CRP concentration between this fever episode and the previous, untreated one (figure 1).

Patient 2

In this 26-year-old woman the diagnosis of HIDS was made three years ago, after she had experienced fever episodes since two months after birth. Childhood vaccinations consistently precipitated febrile attacks. The diagnosis was confirmed by mutation analysis, and an immeasurably low mevalonate kinase enzyme activity (table 1). The attack during which she was monitored appeared to be uncommonly severe with respect to the accompanying symptoms. She did not receive treatment during this attack which lasted seven days; she experienced massive cervical and iliac lymphadenopathy and developed oral and vaginal aphthous ulcers. CRP concentration rose to a maximum of 315 mg/l after 72 hours, while her body temperature was maximally 38.4°C (figure 2A). A subsequent fever episode is depicted in figure 2B. The patient only reached our hospital some 48 hours after onset of symptoms, and immediately after admission etanercept

### Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Age at onset (months)</th>
<th>Mevalonate kinase genotype</th>
<th>Mevalonate kinase enzyme activity</th>
<th>Serum IgD (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>3</td>
<td>V377I/G202R</td>
<td>ND</td>
<td>2330</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>2</td>
<td>V377I/417insC</td>
<td>&lt;0.1%</td>
<td>745</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>1</td>
<td>V377I/I268T</td>
<td>10.7%</td>
<td>616</td>
</tr>
</tbody>
</table>

*Expressed as % of normal; †reference value IgD <100 U/ml; ND = not determined.
treatment was initiated. At that time, serum CRP concentration was similar to that at 48 hours into the first attack (263 vs 252 mg/l), as was her clinical score (74 vs 71 points) (figure 2). After institution of treatment, the CRP concentration declined steadily, and within three days her symptoms had disappeared (figure 2B). Thus, etanercept seemed to shorten this attack in comparison with the previous one. The patient maintained that the second attack was milder and she was unconvinced of a beneficial effect.

Patient 3
Patient 3 is a 38-year-old woman with fever episodes since birth (table 1). She was admitted to the hospital for observation of an untreated fever episode. On admission, she complained of myalgia, arthralgia, abdominal pain and skin lesions. Her body temperature was 36.8°C, but rose to above 39°C within two days (figure 3A). The symptomatic attack persisted for six days, with a concomitant rise and fall of CRP concentration.

Because of a planned trip to China she required several vaccinations, and given her earlier childhood experiences of fever attacks after vaccinations, we decided to admit her for administration of the injections. We gave her one vaccination for hepatitis A (a primo vaccination in her case) and one (repeat) DTP toxin vaccination, separated by one month. Some 24 to 48 hours after administration of each vaccine she developed a characteristic HIDS attack with fever, abdominal pain, myalgia and fatigue. In both instances this was accompanied by an intense acute-phase response (maximum CRP 166 mg/l; figures 3B and 3C).

We used this model of vaccination-precipitated HIDS attack to test the efficacy of early institution of treatment to abort the fever episode. In the first attack, two doses of etanercept (25 mg, subcutaneously) were administered 72 and 86 hours after vaccination (48 and 72 hours after onset of the first symptoms). The symptomatic attack lasted for 5.5 days in total, with maximum CRP concentration reaching 36 hours after the first dose of etanercept (figure 3B). At the next vaccination one month later, we administered anakinra, a recombinant selective IL-1 receptor antagonist (100 mg per dose, subcutaneously), at three time points from 72 hours after vaccination, with an interval of 24 hours. Body temperature normalised and symptoms disappeared within 17 hours after the first injection, peak CRP concen-
Antibody titres were found to be adequate after both vaccinations (data not shown), thus demonstrating that the administration of cytokine antagonists 72 hours after vaccination did not have an influence on the effectiveness of the vaccinations.

**DISCUSSION**

In this pilot study monitoring fever attacks in HIDS, we closely followed seven fever episodes in three patients, with and without intervention.

To quantify the accompanying symptoms of the inflammatory attack, we developed a clinical scoring system consisting of the total scores on a visual analogue scale on a range of 12 symptoms and signs. At the moment the patients felt the onset of a fever attack, they documented a total score of between 20 and 25. Since concentration of CRP and some of the symptoms, most notably tiredness, may persist for a longer period, the end of a HIDS attack may be difficult to define. We found that the proposed clinical score may help with this as well: we suggest defining the end of the attack as the moment at which the clinical score decreases to 20 or less.

The results of monitoring fever episodes in patients 1 and 2 demonstrate the variability of this disorder. It was our aim to start with intervention at the earliest possible moment and we therefore instructed patients to contact us as soon as possible after the start of symptoms. However, even in our small pilot study there was a difference of 36 hours between the time of first administration of etanercept in the two patients. The wide variation seriously impedes the comparability of results in a larger trial set-up. Part of the delay was caused by the fact that we admitted patients to our clinic, which might also induce a selection bias towards more severe attacks. However, treatment at home would make it more difficult to objectively observe symptoms, body temperature and CRP concentrations.

A HIDS patient who needed vaccinations allowed us to observe the power of these vaccinations to provoke a fever episode. In both instances, vaccination resulted in a fever episode within 12 to 24 hours. These attacks were comparable with attacks not precipitated by vaccinations. There are some advantages to using this provocation model: it is simple, easy to use and offers an opportunity to closely monitor the onset of the attack from the very beginning, and thus to standardise the time to starting treatment. Since patients are hesitant to receive (necessary) vaccinations because of the risk of a febrile attack, a closely monitored setting will be helpful to ensure that they do receive them.

With respect to the observations of effect of treatment-on-demand in these patients: these first results appear to be mixed, and this pilot study does not allow us to draw firm conclusions on that point. Anakinra seems to be more...
successful than etanercept; this warrants further examination. HIDS is part of a group of hereditary autoinflammatory syndromes, whose common pathogenic background seems to involve IL-1 signalling. Recently several groups have reported treating hereditary autoinflammatory syndromes successfully with the recombinant form of IL-1ra, anakinra. It remains difficult to get solid evidence on treatment efficacy in orphan diseases, especially when periodic and variable in phenotype, such as HIDS. Most published reports concern clinical observations in one or two patients. Drug trials set up on established lines such as randomised controlled trials will often remain underpowered because of too few patients and too few episodes of illness. Also, because the frequency of fever attacks in adult HIDS patients will usually diminish to between 6 and 12 per year, patients will be more interested in an on-demand treatment which shortens an attack than in continuous treatment (and continuous life-long risk of side effects), unless this continuous treatment will abolish all further symptoms. We suggest that the vaccination provocation model in combination with the clinical score described in this pilot study will offer an opportunity for more rigorous and standardised study of on-demand treatment in HIDS.

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