

Effects of the Histone Deacetylase Inhibitor ITF2357 in Autoinflammatory Syndromes

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We explored the effects of the oral histone deacetylase (HDAC) inhibitor ITF2357 in patients with autoinflammatory syndrome. In this prospective open-label pilot study, eight patients were enrolled; one patient with tumor necrosis factor receptor-associated periodic syndrome (TRAPS), three patients with hyper-IgD and periodic fever syndrome (HIDS) and four patients with Schnitzler syndrome were closely followed during 90 d of ITF2357 treatment. Three patients with Schnitzler syndrome and one TRAPS patient experienced a partial remission. In four patients, there was no effect. In HIDS patients, there was a tendency toward a higher attack frequency and increasing attack severity. In two patients (one TRAPS and one HIDS), we observed a decrease of acute-phase response without signs of clinical improvement. One patient with Schnitzler syndrome showed a partial response despite an ongoing acute-phase response. In conclusion, ITF2357 monotherapy was able to induce partial response only in patients with Schnitzler syndrome and no response in patients with HIDS.

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INTRODUCTION

Autoinflammatory syndromes are a group of disorders characterized by recurrent or chronic inflammation. The inflammation occurs spontaneously or after minor triggers in the absence of autoantibodies and antigen-specific T-cells (1,2). To date, at least eight genetically distinct hereditary autoinflammatory syndromes are known. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and the hyper-IgD and periodic fever syndrome (HIDS) are two of these syndromes. More recently, the acquired disorder Schnitzler syndrome (urticaria, periodic fever and paraproteinemia) has also been recognized as an autoinflammatory syndrome (3,4). Although the genetic mutations for the hereditary autoinflammatory syndromes are known, the pathogenesis of the recurrent inflammatory attacks is not fully

explained. Symptomatic episodes are associated with increased serum concentrations of both proinflammatory cytokines (tumor necrosis factor [TNF]- α , interleukin [IL]-6, IL-1 β and interferon [IFN]- γ) as well as antiinflammatory mediators (IL-1ra, sTNFR p55 and soluble tumor necrosis factor receptor [sTNFR] p75) (5–8). The current concept is that IL-1 β plays a central role in many of these disorders (2,6,9,10).

Thus far, treatment of the recurrent inflammatory episodes in HIDS and TRAPS has been difficult. Amyloidosis is a serious complication of chronic or recurrent inflammation seen in these syndromes (11–13). Therefore, it is important to develop effective treatment options that reduce clinical symptoms and the acute-phase response in patients suffering from these syndromes. Recombinant human IL-1 receptor antagonist

(rhIL-1ra, or anakinra) is effective in refractory TRAPS and HIDS and is remarkably successful in Schnitzler syndrome. The success of this drug underscores the role of IL-1 in the pathogenesis of these disorders. Despite its effectiveness, daily painful subcutaneous injections and reactions at the injection site as well as its short half-life remain a problem (3,14,15).

ITF2357 is an orally active histone deacetylase (HDAC) inhibitor with a potent antiinflammatory effect in preclinical studies. *In vitro* studies show inhibition of TNF- α , IFN- γ and IL-6 production and IL-1 β secretion (16,17). To establish whether ITF2357 is able to modify the clinical symptoms of patients with autoinflammatory syndromes and reduce the acute-phase response in a safe and noninvasive manner, we decided to perform an investigator-initiated open-label pilot study.

PATIENTS AND METHODS

Adult patients with established TRAPS, HIDS and Schnitzler syndrome visiting the outpatient clinic of the Radboud University Nijmegen Medical Centre were eligible for the study. Only pa-

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Table 1. Patient characteristics before the start of ITF2357.

| Patient | Age/sex | Disease | Mutation (gene) | Attack frequency (per month) | Attack duration (days) | Prior medication (mg/day) |
|---------|---------|------------|-------------------|------------------------------|------------------------|--|
| 1 | 24/F | TRAPS | C43Y (TNFRSF1A) | 1.5 | 10–14 | 10 mg prednisolone, anakinra od ^a |
| 2 | 64/M | Schnitzler | — | Continuous | — | 25 mg prednisolone |
| 3 | 61/F | Schnitzler | — | Continuous | — | 100 mg anakinra |
| 4 | 21/F | HIDS | V3771/V3771 (MVK) | 1.5 | 4–8 | Anakinra od |
| 5 | 61/M | Schnitzler | — | Continuous | — | 100 mg anakinra, 5 mg levocetirizin |
| 6 | 38/F | HIDS | V3771/G202R (MVK) | 1.0 | 3–6 | — |
| 7 | 39/F | HIDS | V3771/del (MVK) | 0.5 | 5–10 | — |
| 8 | 69/F | Schnitzler | — | Continuous | — | — |

^aod, on demand.

tients with severe active disease (one or more attack every 8 wks or continuous symptoms) were included. The local ethical committee gave permission for the study, and all patients gave written informed consent. The trial was registered under number 2006-002415-27 in the Clinical Trial Registry. Patients under the age of 18 years, pregnant and lactating women and patients with increased risk for infection, current infection, renal failure (glomerular filtration rate <30 ml/1.73 m²/min) or preexisting malignancy were excluded from participation in the study.

On a daily basis, patients were asked to score the severity of their symptoms on a scale of 1–10 on a symptom score list in Dutch. This symptom score list was introduced and discussed in more detail elsewhere (14). In brief, the scores of one day were added and this number (varying from 0 to 130) is called the clinical score. In continuous symptomatic patients, complete remission required a clinical score <5, the absence of fever (temperature <38.0°C) and normalization of C-reactive peptide (CRP) (<10 mg/L) and white blood cell count (<11 × 10⁹/L). In periodically symptomatic patients, complete remission required the absence of inflammatory attacks. The beginning of an attack was defined by a clinical score >20 and/or a temperature of ≥38.0°C.

The HDAC inhibitor ITF2357 was provided by the manufacturer (Italfarmaco SpA, Cinisello Balsamo, Milan, Italy) as 50-mg capsules. Before start of the study drug, biologicals such as anakinra and etanercept had to be discontinued.

Low-dose prednisolone (maximum 10 mg/day), nonsteroidal antiinflammatory drugs, acetaminophen and oral antihistaminic drugs were allowed. In continuous symptomatic patients, ITF2357 was started when patients were symptomatic after cessation of anakinra or etanercept, and ITF2357 was started in patients with inflammatory attacks when symptomatic or during an asymptomatic period. The initial dose was 50 mg twice a day. If after a minimum of 4 d of treatment there was no complete remission, the dose was increased to 50 mg ITF2357 three times a day. Based on the available toxicology data at the time of the study, treatment was not allowed for >90 d.

Blood was taken from every patient before the start of ITF2357. After start of therapy, patients were seen on our outpatient clinic on day 14, 42, 84 and 126 for evaluation of clinical symptoms, physical examination and blood tests. After cessation of the study drug, the patients were observed for at least 1 month to monitor residual effects of the drug, rebound phenomena and side effects. Patients were instructed to contact the investigator in case of any adverse effect. If patients remained symptomatic during treatment, more regular checkup visits were scheduled.

Ex vivo production of cytokines (IL-6 and IL-1β) was measured as described elsewhere (18). In short, the peripheral blood mononuclear cell fraction was obtained by density centrifugation of diluted heparinized blood (one part blood to one part pyrogen-free saline) over

Ficoll-Paque (Pharmacia Biotech, Uppsala, Sweden). Peripheral blood mononuclear cells were washed twice in saline and suspended in culture medium supplemented with 1% gentamicin, 1% L-glutamine, and 1% pyruvate. The cells were counted in a hemocytometer, and their number was adjusted to 5 × 10⁶ cells/mL. The 5 × 10⁵ peripheral blood mononuclear cells in a volume of 200 μL/well were incubated at 37°C in round-bottom 96-well plates (Greiner, Nurnberg, Germany) with 10 ng/mL highly purified *E. coli* lipopolysaccharide (Sigma) or culture medium alone. After 24 h of incubation, supernatants were collected and stored at –20°C until assayed. IL-1β and IL-6 concentrations were measured in these supernatants by commercial enzyme-linked immunosorbent assay kits (R&D Systems and Sanquin, respectively) according to the manufacturer instructions.

RESULTS

One TRAPS patient, five patients with Schnitzler syndrome and four patients with HIDS were eligible. One Schnitzler patient did not want to participate because of the necessity to discontinue anakinra. One HIDS patient did not want to participate because of the burden of regular hospital visits. Patients with continuous symptoms who had to discontinue or taper their standard medication were admitted to our hospital for close monitoring of the onset of symptoms.

Characteristics of the eight patients enrolled in the study are given in Table 1. The duration of treatment and reasons

Table 2. Side effects and reasons for ITF2357 cessation.

| Patient | Maximum ITF2357 dose (mg/day) | Duration of ITF2357 use (days) | Side effects | Response | Reason why ITF2357 was discontinued |
|---------|-------------------------------|--------------------------------|----------------------------|----------|--|
| 1 | 150 | 15 | Nausea, vomiting, diarrhea | Partial | Recurrence of attack and side effects (decreased CRP and leucocytes) |
| 2 | 150 | 90 | Abdominal pain, nausea | Partial | Complete course |
| 3 | 150 | 6 | | No | Aggravation of clinical symptoms (decreased CRP and leukocytes) |
| 4 | 100 | 3 | | No | More severe attack |
| 5 | 150 | 51 | Epigastric pain, nausea | Partial | Side effects |
| 6 | 100 | 57 | | No | Higher attack frequency and more severe attacks |
| 7 | 100 | 42 | | No | Higher attack frequency and more severe attacks |
| 8 | 150 | 90 | | Partial | Complete course |

for discontinuation are listed in Table 2. As illustrative examples, we report three patients in detail.

Patient 1 has been described previously as the first patient with TRAPS in whom anakinra was shown to be effective (15). She had been treated intermittently with anakinra and also 10 mg prednisolone daily in the period before enrollment. She started 100 mg ITF2357 (1.67 mg/kg) in a single dose each day during an exacerbation, marked by a temperature up to 38.7°C, serositis, myalgia, arthralgia, abdominal complaints, fatigue and a migratory erythematous rash (maximum clinical score 45 on day 1; Figure 1). Initially, fever subsided (day

3), CRP level dropped from 159 to 50 mg/L (day 5) and symptoms improved to a minimum clinical score of 20 (day 4). Physical examination showed no abnormalities apart from a migratory erythematous rash on the abdomen (day 0–4) that disappeared during treatment. After increasing the dose to 150 mg ITF2357 (2.5 mg/kg) on the fourth day, she experienced side effects in the form of abdominal complaints with a maximum side effects score of 19 (nausea, vomiting and diarrhea) on the ninth day, although these symptoms could also indicate a TRAPS exacerbation. The other inflammatory symptoms also worsened and the clinical score rose to a maximum of 35 on day 15 (myalgia, fatigue, anorexia, arthralgia and serosi-

tis). This was accompanied by a rise in CRP levels to 127 mg/L (day 15) and recurrence of fever (maximum temperature 38.6°C on day 13). We concluded an initial partial response followed by an exacerbation and the occurrence of side effects associated with increasing the dose of ITF2357. Therefore, ITF2357 was discontinued after 15 d of treatment.

Patient 8 was known to have Schnitzler syndrome. Before enrollment in this study, she had not received any medication. The patient was started on 100 mg ITF2357 (1.33 mg/kg) in a single daily dose during an exacerbation marked by urticaria, fatigue, myalgia and arthralgia (maximum clinical score 23 on day 2, maximal temperature 38°C on day 1; Figure 2). Maximal CRP and serum amyloid A (SAA) lev-

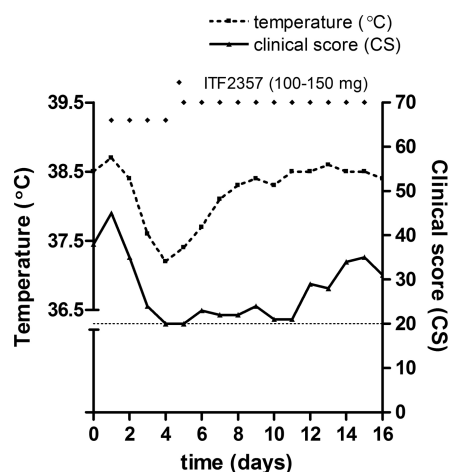


Figure 1. Clinical characteristics of patient 1 (TRAPS) during ITF2357 treatment. See text for details.

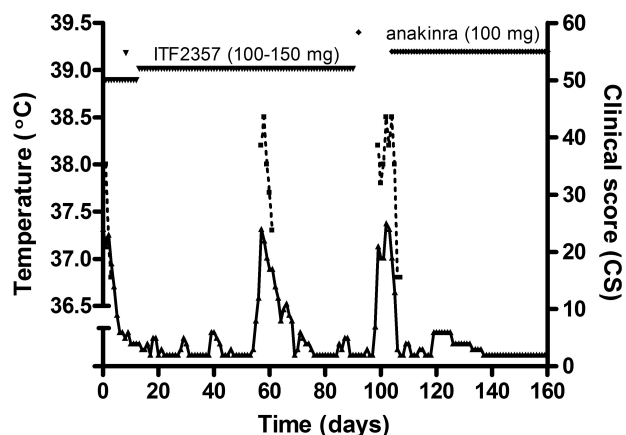


Figure 2. Clinical characteristics of patient 8 (Schnitzler syndrome) during ITF2357 treatment. See text for details.

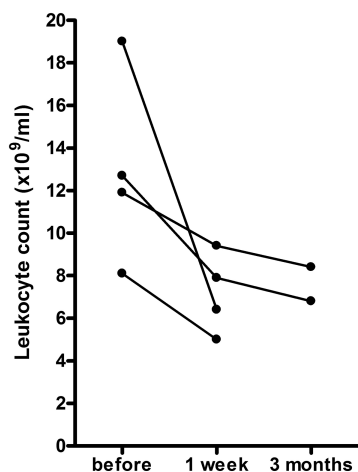


Figure 3. Leukocyte count in four patients with Schnitzler syndrome before the start of ITF2357, after 1 wk and after 3 months.

els were 91 and 200 mg/L, respectively (day 1 and 3). Immediately, the clinical score dropped to ≤ 10 , but since she kept experiencing low-grade urticaria and myalgia, the ITF2357 dose was raised to 150 mg (2 mg/kg) on day 13. CRP, SAA concentrations and platelet counts remained high throughout the treatment period despite clinical improvement. However, the leukocyte count normalized (Figure 3). She experienced two exacerbations with a clinical score >10 . There were no side effects. We concluded a rapid initial response, but during 90 d, the overall response was classified as a partial response. After cessation, the patient experienced an exacerbation, which responded to anakinra.

Patient 6 is a 38-year-old female with HIDS who suffers from typical attacks occurring once a month. Before participation in this study, she had not received any medication. She started 100 mg ITF2357 (1.33 mg/kg) in a single dose on the first day of an HIDS attack (Figure 4). The attack lasted 3 d, with a maximum clinical score of 38 (sore throat, rhinitis, myalgia, arthralgia, lymphadenopathy and fatigue) and temperature of 39.1°C. ITF2357 did not modulate attack severity or duration. During treatment, she experienced two other HIDS attacks. The first attack showed a clinical score of 42 (sore

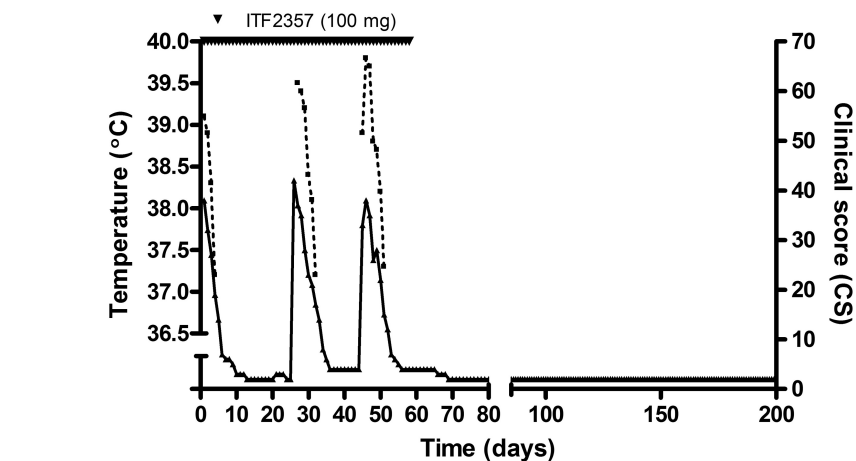


Figure 4. Clinical characteristics of patient 6 (TRAPS) during ITF2357 treatment. See text for details.

throat, rhinitis, myalgia, arthralgia, lymphadenopathy, fatigue and rash) and temperature of 40.1°C; the clinical score of the second attack was 38 (sore throat, rhinitis, myalgia, arthralgia, lymphadenopathy and fatigue), with a CRP of 20 mg/L and temperature of 39.7°C. She felt that these two attacks were more severe and longer than her usual attacks. Therefore, ITF2357 was discontinued after 57 d. We concluded no response. No side effects were reported. During the follow up of 5 months, she only experienced one attack (day 240 maximum clinical score 26, temperature 38°C, CRP level 74 mg/L).

Cytokines Studies

Measurements of the *ex vivo* production of IL-1 β and IL-6 showed highly variable results with wide interindividual variation. No consistent pattern of inhibition was observed during prolonged ITF2357 treatment (data not shown). These observations are consistent with phase I studies in volunteers (19), in which the inhibition of cytokines showed an inhibition during the first 4 h but a return to baseline cytokine production 12 h after ingestion. In this study, we did not take multiple samples during the day.

Side Effects

The side effects noted in our patients are listed in Table 2. The major side ef-

fects were upper-abdominal complaints with nausea and vomiting, which led to premature cessation of treatment in two patients (patients 1 and 5). Hematological abnormalities and disturbances in blood chemistry were not found.

DISCUSSION

In this open-label pilot study of the HDAC inhibitor ITF2357 in eight patients with autoinflammatory disorders (four patients with Schnitzler syndrome, three with HIDS and one with TRAPS), the effect of the drug was disappointing compared with anakinra. We had high expectations on the basis of the inhibition of IL-1 β , TNF- α , IL-6 and IFN- γ but not IL-1Ra *ex vivo* in volunteers (19). The anticipated responses were expected to be similar to those of anakinra but were not. Nevertheless, there were objective as well as subjective findings that ITF2357 in some patients did initially reduce the severity of systemic inflammation. However, these were short-lived and, as monotherapy, not sufficient to replace parenteral administration of anakinra and, in recent trials, antibodies to IL-1 β .

Although we observed partial remission in patients 1, 2, 5 and 8, there were no responses in the other four. All three HIDS patients were nonresponders and, in fact, in HIDS patients, there was even a tendency toward a higher attack fre-

quency and increasing attack severity (patients 4, 6 and 7). In two patients, we observed an effect on the markers of the acute-phase response without signs of clinical improvement (patients 1 and 3), and in one patient (patient 8), there was a partial response despite an ongoing acute-phase response.

How can we explain the relatively disappointing results? First, they may have been caused by the selection of diseases. From the successes of anakinra in Schnitzler syndrome and HIDS (and to a lesser extent in TRAPS), the conclusion is that these are typical IL-1 β diseases (3,14, 15,20). Looking at the effects of ITF2357 on cytokine production *ex vivo* in volunteers, the conclusion may be drawn that the effects on TNF, IL-6 and IFN- γ are most impressive and occur at the level of lipopolysaccharide-induced cytokine synthesis. In the case of IL-1 β , the reduction in this cytokine is not at the level of gene expression or synthesis of the precursor but at the level of secretion (17). Extrapolated to the situation *in vivo*, this might mean that with an ongoing inflammatory drive, pro-IL-1 β accumulates intracellularly and may be even converted to bioactive cytokine, without being secreted when exposed to ITF2357. Cells replete with IL-1 β may act as cytokine time bombs, releasing much bioactive IL-1, for instance, when a concomitant stimulus arises.

Another explanation is that preceding anakinra treatment in patients with Schnitzler syndrome may have led to up-regulated IL-1 receptor type 1, which sensitizes cells as a target for cytokine action. Patients 2 and 8 had never received anakinra before ITF2357 and were the only patients who completed the trial with a satisfactory response. This hypothesis may not apply to HIDS, since two nonresponsive HIDS patients did not receive anakinra in the 2 years before participating in this study (6,7).

We did not detect major changes in *ex vivo* production of IL-1 β and IL-6 in the days and weeks after the treatment. This is consistent with the cytokine studies in human volunteers, in which cytokine

production, especially of IL-6, was inhibited over a period of 8–12 h, starting 2 h after oral intake; 12 h after the intake of the drug, the cytokine production was again at baseline. Our studies do not support a cumulative effect on cytokine production.

The side effects of ITF2357 were relatively mild, but led to cessation of the drug in two patients (patients 1 and 5); this should probably be viewed in face of the relative ineffectiveness.

Where should we go from here? We conclude that a larger (controlled) clinical trial of ITF2357 monotherapy in the autoinflammatory diseases is not warranted. However, ITF2357 may be considered as a steroid-sparing drug in combination with low-dose steroids. In children with systemic-onset juvenile idiopathic arthritis, a disease highly responsive to IL-1 β blockade, ITF2357 was administered at a dose of 1.5 mg/kg in two divided doses for 12 wks with excellent safety (21). In that study, there was a significant reduction in joint inflammation after 12 wks of therapy, which extended beyond cessation of the drug, and there was a reduction in the elevated white blood cell count and neutrophil count within 2 wks of initiation of therapy (22), similar to some of the patients studied in this report (see Figure 3). It appears that there is a limited but consistent early response to ITF2357 in a reduction in objective markers of systemic inflammation in both studies, which might represent a reduction in either IL-1 β or IL-6.

From the present study, we conclude that increasing the dose of ITF2357 to >1.5 mg/kg appears to increase gastrointestinal side effects or even worsen disease severity. If ITF2357 is to be considered for chronic therapy, dosing of 1.5 mg/kg in two divided doses per day is likely to minimize any side effects and is required to enable prolonged use. In the present study, however, the objective as well as the clinical responses to an oral HDAC inhibitor such as ITF2357 are not as impressive as those after anakinra or canakinumab administration.

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DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

REFERENCES

- McDermott MF, *et al.* (1999) Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell*. 97:133–44.
- Masters SL, Simon A, Aksentijevich I, Kastner DL. (2009) Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. *Annu. Rev. Immunol.* 27:621–68.
- de Koning HD, *et al.* (2006) Beneficial response to anakinra and thalidomide in Schnitzler's syndrome. *Ann. Rheum. Dis.* 65:542–4.
- de Koning HD, Bodar EJ, van der Meer JW, Simon A. (2007) Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin. Arthritis. Rheum.* 37:137–48.
- Drenth JPH, van Deuren M, van der Ven-Jongekrijg J, Schalkwijk CG, van der Meer JWM. (1995) Cytokine activation during attacks of the hyperimmunoglobulinemia D and periodic fever syndrome. *Blood*. 85:3586–93.
- Frenkel J, *et al.* (2002) Lack of isoprenoid products raises *ex vivo* interleukin-1 β secretion in hyperimmunoglobulinemia D and periodic fever syndrome. *Arthritis Rheum.* 46:2794–803.
- Nowlan ML, *et al.* (2006) Systemic cytokine levels and the effects of etanercept in TNF receptor-associated periodic syndrome (TRAPS) involving a C33Y mutation in TNFRSF1A. *Rheumatology (Oxford)*. 45:31–7.
- Rebelo SL, *et al.* (2006) Modeling of tumor necrosis factor receptor superfamily 1A mutants associated with tumor necrosis factor receptor-associated periodic syndrome indicates misfolding consistent with abnormal function. *Arthritis Rheum.* 54:2674–87.
- Aksentijevich I, *et al.* (2002) De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding fam-

- ily of pyrin-associated autoinflammatory diseases. *Arthritis Rheum.* 46:3340–8.
10. Chae JJ, *et al.* (2003) Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. *Mol. Cell.* 11:591–604.
 11. Cefle A, *et al.* (2005) A comparison of clinical findings of familial Mediterranean fever patients with and without amyloidosis. *Rheumatol. Int.* 25:442–6.
 12. Hull KM, *et al.* (2002) The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. *Medicine (Baltimore).* 81:349–68.
 13. van der Hilst JC, Simon A, Drenth JP. (2005) Hereditary periodic fever and reactive amyloidosis. *Clin. Exp. Med.* 5:87–98.
 14. Bodar EJ, van der Hilst JC, Drenth JP, van der Meer JW, Simon A. (2005) Effect of etanercept and anakinra on inflammatory attacks in the hyper-IgD syndrome: introducing a vaccination provocation model. *Neth. J. Med.* 63:260–4.
 15. Simon A, *et al.* (2004) Beneficial response to interleukin 1 receptor antagonist in traps. *Am. J. Med.* 117:208–10.
 16. Leoni F, *et al.* (2005) The histone deacetylase inhibitor ITF2357 reduces production of pro-inflammatory cytokines in vitro and systemic inflammation in vivo. *Mol. Med.* 11:1–15.
 17. Carta S, *et al.* (2006) Histone deacetylase inhibitors prevent exocytosis of interleukin-1beta-containing secretory lysosomes: role of microtubules. *Blood.* 108:1618–26.
 18. Simon A, *et al.* (2004) Simvastatin treatment for inflammatory attacks of the hyperimmunoglobulinemia D and periodic fever syndrome. *Clin. Pharmacol. Ther.* 75:476–83.
 19. Furlan A, *et al.* (2011) Pharmacokinetics, safety and inducible cytokine responses during a phase 1 trial of the oral histone deacetylase inhibitor ITF2357 (givinostat). *Mol. Med.* 17:353–362.
 20. Hoffman HM, *et al.* (2004) Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. *Lancet.* 364:1779–85.
 21. Vojinovic J, *et al.* (2011) Safety and efficacy of an oral histone deacetylase inhibitor in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum.* 63:1452–8.
 22. Vojinovic J, Damjanov N. (2011) HDAC inhibition in rheumatoid arthritis and juvenile idiopathic arthritis. *Mol. Med.* 17:397–403.