# Controlling Inflammation
## Contemporary Treatments for Autoinflammatory Diseases and Syndromes

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**KEYWORDS**

• Autoinflammation • Treatment • Anakinra

**KEY POINTS**

- The initial therapy for all of the autoinflammatory syndromes is the control of fever, pain, or the symptoms derived from the inflammatory reaction.
- The initial effort should focus on making the precise diagnosis. This strategy facilitates the choice of appropriate initial therapy, which has been defined for many of these syndromes and diseases.
- Accurate diagnosis is often difficult; rendering symptom management the mainstay of initial therapy while the definitive diagnosis remains elusive.
- Steroids are not considered useful in the autoinflammatory syndromes, yet they still play an important role in the early treatment of these diseases.
- Colchicine has been approved for the treatment of familial Mediterranean fever and its late complications.
- Antitumor necrosis factor therapy has been used and proved useful in several autoinflammatory diseases.
- The most recent acquisition for the treatment of autoinflammatory syndromes is anti-interleukin 1, anakinra, rilonacept, and canakinumab, with good results in many of the autoinflammatory syndromes.
- New molecules and pathways of disease will facilitate the development of effective therapies.

## INTRODUCTION

The autoinflammatory disorders are an expanding group of diseases characterized by recurrent systemic inflammation in the absence of infection, autoantibodies, or antigen-specific T cells; they are thus probably related to a primary dysfunction of the innate immune system, with no adaptive immune deregulation. Dysfunction of the innate immune system includes abnormal responses to pathogens associated with the lipopolysaccharide and peptidoglycan of myeloid cells, such as neutrophils and monocytes in blood and tissues, in addition to the dysregulation of inflammatory cytokines and their receptors, like interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), and others[1]; thus, these substances and molecules have become the targets for present and future therapies.

The autoinflammatory diseases include hereditary disorders like: familial Mediterranean fever (FMF), mevalonate kinase (MK) deficiency, tumor necrosis factor receptor–associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome

Neither of the authors has any financial conflicts.
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Dermatol Clin 31 (2013) 507–511
http://dx.doi.org/10.1016/j.det.2013.04.007
0733-8635/13/$ – see front matter 

(MWS), chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome, Blau syndrome, hyperimmunoglobulin D syndrome (HIDS), pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, chronic recurrent multifocal osteomyelitis; some multifactorial disorders like Crohn and Behçet disease, juvenile idiopathic arthritis (JIA), adult Still disease, and macrophage activation syndrome (MAS) are considered autoinflammatory diseases; so are periodic fever, aphthous stomatitis, and adenopathy (PFAPA) syndrome and Majeed syndrome.

## TREATMENT

The initial therapy for all the autoinflammatory syndromes is the control of fever, pain, or the symptoms derived from the inflammatory reaction. Antiinflammatory medications are the initial choice; nonsteroidal antiinflammatory drugs (NSAIDs) have been used with variable success for decades; so have systemic steroids.

The initial effort should focus on making the precise diagnosis. This goal facilitates the choice of appropriate initial therapy, which has been defined for many of these syndromes and diseases. Accurate diagnosis is often difficult, rendering symptom management the mainstay of initial therapy while the definitive diagnosis remains elusive.

Chronic management includes symptom management and prevention of complications of long-term disease and treatment, including amyloidosis and premature coronary artery disease (**Table 1**).

### *Nonspecific Medications*

The initial drug management includes corticosteroids or nonsteroidal medications, as well as others with antiinflammatory effects, as follows.

### *Cimetidine*

Cimetidine is a histamine 2 ($H_2$) receptor antagonist that inhibits stomach acid production. Used to treat and reduce the symptoms of gastritis and peptic ulcer disease, it has been shown debatably useful in the treatment of herpes simplex 1 and 2, herpes zoster virus, common warts, some inflammatory conditions associated with calcifications, and so forth. It has also been used to modify epidermal growth factor, vascular endothelial growth factor, and E-selectin, for the treatment of several cancers and their metastasis. Cimetidine was shown to be of some benefit in the pain of interstitial cystitis. Cimetidine has been used in PFAPA syndrome, with resolution of the fever and some of the other manifestations of the syndrome; at a dose of 20 mg/kg/d, cimetidine has a response greater than 50%; the mechanism of action is not known, but has been linked to inhibition of T-suppressor cells by blocking $H_2$-receptors, with minimal side effects.[2,3]

### *Statins*

The involvement of MK in the cholesterol synthesis pathway encouraged the introduction of statins in the management of MK deficiency and HIDS; good results were obtained in a small group of patients.[4] MK plays an essential role in the cholesterol synthesis pathway; during cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (the enzyme inhibited by statins) converts HMG-CoA to mevalonate. This conversion is blocked when a mutation in the MVK gene exists and mevalonate is not converted to mevalonate phosphate, causing an increase in mevalonic acid in serum, tissues, and urine. The absence of a negative feedback loop, naturally provided by the presence of the end products of synthesis, leads to increased HMG-CoA reductase activity, consequently increasing serum, tissue, and urine levels of mevalonic acid. The inhibition of MK also activates caspase 1 and decreases isoprenoids, which increase IL-1β. The blockade of these mediators may soon help to clarify the pathophysiology of these diseases.

### *NSAIDs*

NSAIDs are nonselective inhibitors of cyclooxygenase, acting on both isoenzymes Cox1 and Cox2, causing a reversible inhibition, which is in contrast

**Table 1**
**Overall summary of hereditary periodic fever syndromes**

| Feature | FMF | HIDS | TRAPS | MWS | FCU | CINCA |
|---|---|---|---|---|---|---|
| Treatment | Colchicine to prevent attacks and for long-term prevention of amyloidosis | Supportive NSAIDs, prednisone, simvastatin | NSAIDs and steroids, anti-TNF, anti-IL-1 | NSAIDs and steroids, anti-IL1 | Anti-IL-1 | Anti-IL-1 |

*Abbreviations:* FCU, familial cold urticaria; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome.