Pearls from the Third Israeli Conference on FMF, Other Autoinflammatory Disorders and AA Amyloidosis

Avi Livneh MD[1,3] and Ilan Ben-Zvi MD[1,2,3]

[1]Heller institute of Medical Research, Department of Internal Medicine F and Rheumatology Unit, Sheba Medical Center, Tel Hashomer, Israel
[2]Borenstein Talpiot Medical Leadership Program, Sheba Medical Center, Tel Hashomer, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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The third Israeli national conference on familial Mediterranean fever, other autoinflammatory diseases and reactive amyloidosis was held at Sheba Medical Center in July 2013. The title of this conference is different to that of previous meetings, alluding to the increasing attention given nowadays by experts in the field to a series of new disorders, clustered under the heading of autoinflammatory diseases. These diseases, of which more than 10 have already been clinically and genetically well defined [1-5], simulate FMF yet express a highly unique phenotype, allowing a meticulous physician to clinically suspect a diagnosis distinct from FMF and seek confirmation in a diagnostic laboratory or specialized center. Table 1 presents the manifestations and the gene involved in these different diseases. In all these entities the exact pathogenesis has yet to be elucidated, but the gene involved is clearly associated with innate immunity. In a large number of these conditions, interleukin-1 beta antagonists were shown to ameliorate the disease, reducing the severity of its manifestations [Table 1].

Most autoinflammatory conditions are monogenic, resulting from a mutation in a single gene. But there are other well-established autoinflammatory conditions that are not monogenic but have strong linkage to the monogenic conditions. These polygenic disorders carry a phenotype which closely resembles that of the monogenic diseases. One of these entities is Behcet's disease. At the conference, Prof. Ahmet Gul presented a comprehensive review on the new genetic revelations of this syndrome, one being its association with the *MEFV* mutation: M694V [6]. This mutation, in its homozygous state, causes severe FMF [7]. Carriage of one copy of the *MEFV* mutation M694V was linked long ago to Behcet's disease by us [8] and others [9,10]. The high co-occurrence of Behcet's disease with FMF in the same patient and within FMF families was also noted [11].

Prof. Gul devoted the second part of his presentation to FMF, reviewing current and new treatments, focusing particularly on inadequate response to colchicine treatment [12]. The pathogenesis of colchicine failure is not fully understood. Prof. Gul suggested that it be viewed as a consequence of an imbalance created either by an excessive inflammation, overcoming the capacity of colchicine prophylaxis, or by a reduced ability of colchicine to respond to the inflammatory assault. To answer the challenge of intractable FMF, novel treatments targeted at the core of the pathogenic mechanism believed to cause FMF, IL-1β, have been suggested. The role of IL-1β blockers in colchicine-resistant FMF was reviewed at the meeting and is presented in the current issue of *IMAJ* [12].

The current support for IL-1β blockers in the treatment of FMF is poor. A controlled study was published only for one drug, rilonacept, which demonstrated significant efficacy [13]. All manufacturers of existing preparations decline to include FMF in drug indications, mainly due to the lack of controlled studies, despite sufficient published case series implying their favorable effect. An interim report of a placebo-controlled study of anakinra, an IL-1β receptor blocker, for the treatment of colchicine-resistant adult FMF, performed at Sheba Medical Center, was presented at the conference and is reported by Ben-Zvi et al. in the present issue of this journal [14].

The genetics of FMF is a fascinating subject and our understanding of the role of *MEFV* mutations is growing. At this conference, Prof. Elon Pras, who played a major role in mapping and cloning the FMF gene (*MEFV*) [15,16], described the current status of the gene. Interestingly, he pointed out that although FMF is considered a recessively inherited disease, the carriage of only one mutated *MEFV* allele may be associated with an FMF phenotype, usually of milder severity. His presentation at the meeting of the past and present status of our knowledge on *MEFV* appears in this issue of the journal [17].

Finally, AA amyloidosis is the most dreaded complication of all the autoinflammatory diseases and the main cause of mortality in FMF. It became clear years ago that in addition to AA, a fragment of the plasma serum amyloid A protein (SAA), one can detect another plasma protein in the amyloid sediment, called serum amyloid P (SAP). Interestingly, SAP does not favor AA amyloid alone but rather deposits universally in all other amyloid types. Prof. Sir Mark Pepys's group made use of this feature of SAP in diagnostic tests and is

FMF = familial Mediterranean fever

IL-1β = interleukin-1 beta

Table 1. Monogenic autoinflammatory disorders

Disorder	Clinical manifestations	Genetics	Treatment
FMF	Febrile attacks lasting 1–4 days, accompanied by abdominal pain (peritonitis), chest pain (pleuritis), joint pain (monoarthritis) and ELE Chronic: amyloidosis, anemia (normo or microcytic), splenomegaly, exertional leg pain	MEFV mutations, mostly recessive inheritance, FMF may occur in 10% of heterozygotes	Colchicine, IL-1β blockers
TRAPS	Febrile attacks lasting ≥ 1 week, accompanied by migratory ELE-like rash, with limb pain, abdominal pain (peritonitis), pleuritic chest pain, arthritis (large joints), conjunctivitis and periobital edema Chronic: anemia, splenomegaly, amyloidosis	TNFRSF1A, dominant	Steroids, TNF blockers, IL-1β blockers
HIDS	Febrile attacks, lasting 3–7 days, accompanied by maculopapular skin rash, enlarged cervical lymph nodes, arthralgia and symmetric polyarthritis, abdominal pain (peritonitis + diarrhea)	MVK, recessive	Steroids, IL-1β blockers
MWS	Febrile attacks, lasting 1–3 days, accompanied by urticaria-like rash, conjunctivitis, abdominal pain and arthralgia Chronic: sensory neural hearing loss, amyloidosis, continuous rash and without fever	NLRP3, dominant	IL-1β blockers
FCAS	Cold-induced attacks (even minor exposure), occasionally with fever, other signs and symptoms as in MWS	NLRP3, dominant, familial clusters	IL-1β blockers
CINCA/ NOMD	Febrile episodes of short duration, with increase of some chronically lasting symptoms/signs, particularly skin rash Chronic: urticaria-like rash, meningitis, mental retardation, papilledema, deafness, uveitis, conjunctivitis, arthritis of large joints, contractures	NLRP3, dominant, sporadic	IL-1β blockers
PAPA	Episodic, post-trauma papulopustule rash, evolving within days to necrotic ulcers, episodic acneformic pustules and episodic arthritis	PSTPIP1/CD2BP, dominant	
Schnitzler syndrome	Episodic fever of 1–2 day duration, urticarial rash, arthralgia or arthritis Chronic: lymphadenopathy, splenomegaly, bone pain, monoclonal IgM gammopathy		IL-1β blockers,steroids
Majeed syndrome	Episodic fever of 1–3 day duration Chronic: recurrent multifocal sterile osteomyelitis, causing bone pain and limb swelling, dyserythropoietic anemia	LPIN2, recessive	IL-1β blockers, steroids
Blau syndrome	Occasional febrile, episodic rash, arthritis and uveitis Chronic: granulomatous liver, cardiac and kidney disease, cranial neuropathies	NOD2, dominant	Steroids, TNF blockers, IL-1β blockers
DIRA	Afebrile Chronic: pustular and ichtioformic rash, multifocal osteolytic lesions	IL-1 RN, recessive	IL-1β blockers

FMF = familial Mediterranean fever, ELE = erysipelas-like erythema, *MEFV* = MEditerranean FeVer gene, IL-1β = interleukin 1 beta, TRAPS = tumor necrosis factor (TNF) receptor-associated periodic syndrome, TNFRSF1A = tumor necrosis factor receptor superfamily member 1A, HIDS = hyper-immunoglobulin D syndrome, MVK = mevalonic kinase, MWS = Muckle-Wells syndrome, NLRP3 = Nod-like receptor with pyrin domain 3, FCAS = familial cold-associated syndrome, CINCA/NOMID = chronic infantile neurological cutaneous and articular/ neonatal onset multisystem inflammatory disease syndrome, PAPA = pyogenic arthritis, pyoderma gangrenosum, and acne, IgM = immunoglobulin M, NOD2 = nucleotide-binding oligomerization domain-containing protein 2, DIRA = deficiency of interleukin-1-receptor antagonist, IL-1RN = interleukin 1 receptor antagonist

currently utilizing it as a therapeutic target. In this issue of *IMAJ*, Prof. Sir Pepys, who was recently knighted by the Queen of England for his outstanding scientific achievements, presents his lecture on targeted treatment for amyloidosis, focusing on his recent breakthrough innovation that may lead to a cure for AA amyloidosis [18]. Implementing his finding in humans holds enormous promise as a potential cure for this devastating disease.

Corresponding author:
Dr. A. Livneh MD
Dept. of Medicine F, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2476
Fax: (972-3) 530-2114
email: Avi.livneh@sheba.health.gov.il

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