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...
Table 1. Monogenic autoinflammatory disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical manifestations</th>
<th>Genetics</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>FMF</td>
<td>Febrile attacks lasting 1–4 days, accompanied by abdominal pain (peritonitis), chest pain (pleuritis), joint pain (monarthropathy) and ELE</td>
<td>MEFV mutations, mostly recessive inheritance, FMF may occur in ≤ 10% of heterozygotes</td>
<td>Colchicine, IL-1β blockers</td>
</tr>
<tr>
<td>TRAPS</td>
<td>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 periorbital edema</td>
<td>TNFRSF1A, dominant</td>
<td>Steroids, TNF blockers, IL-1β blockers</td>
</tr>
<tr>
<td>HIDS</td>
<td>Febrile attacks lasting 3–7 days, accompanied by maculopapular skin rash, enlarged cervical lymph nodes, arthralgia and symmetric polyarthralgia, abdominal pain (peritonitis + diarrhea)</td>
<td>MVK, recessive</td>
<td>Steroids, IL-1β blockers</td>
</tr>
<tr>
<td>MWS</td>
<td>Febrile attacks, lasting 1–3 days, accompanied by urticaria-like rash, conjunctivitis, abdominal pain and arthralgia</td>
<td>NLRP3, dominant</td>
<td>IL-1β blockers</td>
</tr>
<tr>
<td>FCAS</td>
<td>Cold-induced attacks (even minor exposure), occasionally with fever, other signs and symptoms as in MWS</td>
<td>NLRP3, dominant, familial clusters</td>
<td>IL-1β blockers</td>
</tr>
<tr>
<td>CINCA/ NOMD</td>
<td>Febrile episodes of short duration, with increase of some chronically lasting symptoms/signs, particularly skin rash</td>
<td>NLRP3, dominant, sporadic</td>
<td>IL-1β blockers</td>
</tr>
<tr>
<td>PAPA</td>
<td>Episodic, post-trauma papulopustule rash, evolving within days to nectric ulcers, episodic acnemiform pustules and episodic arthritis</td>
<td>PSTPIP1/CD2BP, dominant</td>
<td>IL-1β blockers</td>
</tr>
<tr>
<td>Schnitzler syndrome</td>
<td>Episodic fever of 1–2 day duration, urticarial rash, arthralgia or arthritis</td>
<td>IL-1β blockers, steroids</td>
<td>IL-1β blockers</td>
</tr>
<tr>
<td>Majeed syndrome</td>
<td>Episodic fever of 1–3 day duration, Chronic: recurrent multifocal sterile osteomyelitis, causing bone pain and limb swelling, dyserythropoietic anemia</td>
<td>LPIN2, recessive</td>
<td>IL-1β blockers, steroids</td>
</tr>
<tr>
<td>Blau syndrome</td>
<td>Occasional febrile, episodic rash, arthritides and uveitis Chronic: granulomatous liver, cardiac and kidney disease, cranial neuropathies</td>
<td>NOD2, dominant</td>
<td>Steroids, TNF blockers, IL-1β blockers</td>
</tr>
<tr>
<td>DIRA</td>
<td>Afebrile Chronic: pustular and ichthioform rash, multifocal osteolytic lesions</td>
<td>IL-1RN, recessive</td>
<td>IL-1β blockers</td>
</tr>
</tbody>
</table>

FMF = familial Mediterranean fever, ELE = erysipelas-like erythema, MEFV = MeDiteranean 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, 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 Pepsy, 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.

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