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ORIGINAL ARTICLE

International Retrospective Chart Review of Treatment Patterns in Severe Familial Mediterranean Fever, Tumor Necrosis Factor Receptor–Associated Periodic Syndrome, and Mevalonate Kinase Deficiency/ Hyperimmunoglobulinemia D Syndrome

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Objective. **Periodic fever syndrome (PFS) conditions are characterized by recurrent attacks of fever and localized inflammation. This study examined the diagnostic pathway and treatments at tertiary centers for familial Mediterranean fever (FMF), tumor necrosis factor receptor–associated periodic syndrome (TRAPS), and mevalonate kinase deficiency (MKD)/hyperimmunoglobulinemia D syndrome (HIDS).**

Methods. **PFS specialists at medical centers in the US, the European Union, and the eastern Mediterranean participated in a retrospective chart review, providing de-identified data in an electronic case report form. Patients were treated between 2008 and 2012, with at least 1 year of followup; all had clinical and/or genetically proven disease and were on/ eligible for biologic treatment.**

Results. **A total of 134 patients were analyzed: FMF (n = 49), TRAPS (n = 47), and MKD/HIDS (n = 38). Fever was commonly reported as severe across all indications. Other frequently reported severe symptoms were serositis for FMF patients and elevated acute-phase reactants and gastrointestinal upset for TRAPS and MKD/HIDS. A long delay from disease onset to diagnosis was seen within TRAPS and MKD/HIDS (5.8 and 7.1 years, respectively) compared to a 1.8-year delay in FMF patients. An equal proportion of TRAPS patients first received anti–interleukin-1 (anti-IL-1) and anti–tumor necrosis factor (anti-TNF) biologic agents, whereas IL-1 blockade was the main choice for FMF patients resistant to colchicine and MKD/HIDS patients. For TRAPS patients, treatment with anakinra versus anti-TNF treatments as first biologic agent resulted in significantly higher clinical and biochemical responses ($P = 0.03$ and $P < 0.01$, respectively). No significant differences in responses were observed between biologic agents among other cohorts.**

Conclusion. **Referral patterns and diagnostic delays highlight the need for greater awareness and improved diagnostics for PFS. This real-world treatment assessment supports the need for further refinement of treatment practices.**

INTRODUCTION

Periodic fever syndrome (PFS) conditions are characterized by attacks of clinical and biochemical inflammation. They are often associated with genetic defects in the innate immune system and follow a chronic disease course; patients may experience the sequelae of persistent inflammation (1,2). The 3 most widely known PFS conditions are under the scope of the present study: familial Mediterranean fever (FMF), tumor necrosis factor receptor–associated periodic syndrome (TRAPS), and mevalonate kinase deficiency (MKD)–associated

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Significance & Innovations

- This study is one of the largest, and most geographically dispersed, retrospective analyses of clinically diagnosed periodic fever syndrome patients who are currently being treated for severe familial Mediterranean fever (FMF), tumor necrosis factor receptor–associated periodic syndrome (TRAPS), and mevalonate kinase deficiency (MKD)/hyperimmunoglobulinemia D syndrome (HIDS).
- A long delay from disease onset to diagnosis was seen within TRAPS and MKD/HIDS (5.8 and 7.1 years, respectively) compared to a 1.8-year delay in FMF.
- An equal proportion of TRAPS patients first received anti–interleukin-1 (anti-IL-1) and anti–tumor necrosis factor (anti-TNF) biologic agents, whereas IL-1 blockade was the main choice for FMF and MKD/HIDS patients.
- For TRAPS patients, treatment with anakinra versus anti-TNF treatments as a first biologic agent resulted in significantly higher clinical and biochemical responses ($P = 0.03$ and $P < 0.01$, respectively). Therefore, we recommend the use of IL-1 inhibition over TNF inhibition in TRAPS patients as a first biologic agent, based on findings from this study and other existing literature. No significant differences in responses were observed between biologic agents among other cohorts.

periodic syndrome (also known as hyperimmunoglobulinemia D syndrome [HIDS]). Although they have different clinical features and etiology, all 3 are characterized by intermittent attacks, fever, and high acute-phase reactants (3). Outside the eastern Mediterranean region, each has a very low prevalence (4,5) and is considered a rare disease. Recent recommendations from Single Hub and Access point for pediatric Rheumatology in Europe have focused on the clinical management of TRAPS, MKD/HIDS, and cryopyrin-associated periodic syndromes, but have referenced a lack of evidence investigating patient treatment experience and outcomes (6). This international study was designed to analyze real-life data to describe the diagnostic pathway, referral patterns to tertiary centers, and subsequent treatment by specialists.

PATIENTS AND METHODS

Data source. Medical centers in the US, European Union (France, Germany, Italy, The Netherlands, and the UK), and the eastern Mediterranean (Israel and Turkey) that specialized in treatment of PFS were invited to participate in this retrospective study. A uniform data set was collected from the medical records of eligible subjects via case report forms. The study was granted Institutional Review Board ethical approval by the partnering institutions as needed and complied with International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, the Declaration of Helsinki, and local laws. Data collection followed data privacy regulations in each country.

Subject inclusion criteria. Subjects (both children and adults) who met all of the following inclusion criteria were considered for enrollment: a clinically and/or genetically confirmed diagnosis of severe FMF, TRAPS, or MKD/HIDS; treated by a specialist physician for the relevant disease at

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Table 1. Patient clinical characteristics at disease onset and diagnosis*

	FMF (n = 49)†	TRAPS R92Q (n = 6)‡	TRAPS (n = 41)‡	MKD/HIDS (n = 38)‡
Age at disease onset, years	2.0 (0.1–29.5)	10.4 (0.3–37.7)	7.4 (0.5–52.9)	0.5 (0.0–8.0)
Age at disease diagnosis, years	4.9 (0.5–31.0)	10.9 (2.0–40.7)	27.6 (0.6–76.3)	8.9 (0.8–46.0)
Delay in diagnosis, years	1.9 (0.0–21.7)	1.4 (0.3–11.7)	5.8 (0.0–75.8)	7.1 (0.5–45.5)
Frequency of flares at disease onset, yearly				
Fever attacks§	26.0 (4.0–60.8)	12.0 (1.0–36.5)	6.0 (2.0–120.0)	12.0 (4.0–36.5)
Total no.	43	5	29	35
Arthritic attacks§	12.0 (6.0–52.0)	12.0 (12.0–12.0)	7.3 (3.0–12.0)	12.5 (4.0–36.5)
Total no.	19	1	8	8
Duration of flares at disease onset, days				
Fever attacks§	3.0 (1.0–21.0)	3.0 (1.0–42.0)	14.0 (4.0–35.0)	5.0 (2.0–20.0)
Arthritic attacks§	3.0 (1.5–7.0)	7.0 (7.0–7.0)	8.5 (5.0–28.0)	7.5 (4.0–20.0)
Severe symptoms at disease onset, no. (%)¶				
Fever	19 (39)	3 (50)	18 (44)	33 (87)
Rash	–	2 (33)	6 (15)	5 (13)
Arthritis (excluding arthralgia)	14 (29)	–	2 (5)	1 (3)
Serositis	26 (53)	3 (50)	10 (24)	5 (13)
Elevated acute-phase reactants (e.g., CRP and/or SAA)	13 (27)	3 (50)	22 (54)	30 (79)
Fatigue	6 (12)	2 (33)	12 (29)	18 (47)
Painful lymph nodes	–	–	2 (5)	18 (47)
GI upset#	19 (39)	1 (17)	17 (41)	19 (50)

* Values are the median (range) unless indicated otherwise. FMF = familial Mediterranean fever; TRAPS = tumor necrosis factor receptor–associated periodic syndrome; MKD = mevalonate kinase deficiency; HIDS = hyperimmunoglobulinemia D syndrome; CRP = C-reactive protein; SAA = serum amyloid A protein.
† Countries presented in table for FMF cohort: France, Germany, The Netherlands, UK, Israel, and Turkey.
‡ Countries presented in table for TRAPS and MKD/HIDS cohorts: US, France, Germany, The Netherlands, UK, Israel, and Turkey.
§ Fever and arthritic attacks can occur simultaneously.
¶ Severity characterized as response of severe and very severe based on physician characterization.
# Multiple options for GI upset could be selected, including abdominal pain, loss of appetite, nausea/vomiting, and diarrhea.

any point between 2008 and 2012, with a minimum length of followup after diagnosis of at least 12 months; and either eligible for, or receiving, treatment with biologic therapy.

Specific criteria defined inadequate disease control for FMF, TRAPS, and MKD/HIDS, thereby suggesting patients eligible for a biologic agent. For this study, FMF patients were required to have an inadequate response to colchicine, defined as either a minimum of 1 typical acute attack per month for at least 3 consecutive months, or continued attacks in a patient compliant with, or intolerant to, effective doses of colchicine. TRAPS patients were required to show inadequate disease control with corticosteroids prior to receiving effective biologic therapy, defined as >6 episodes per year or elevated C-reactive protein (CRP) level >10 mg/liter and/or serum amyloid A protein (SAA) >10 mg/liter between attacks. Lastly, inadequate control for MKD/HIDS referred to patients having a history of ≥3 febrile acute flares in a 6-month period when not receiving prophylaxis treatment, with a duration of each flare ≥4 days and limitation of normal daily activities or elevated CRP level >10 mg/liter and/or SAA >10 mg/liter in between attacks. Treatment efficacy and duration data were not collected for patients enrolled in an interventional clinical trial or following the initiation of canakinumab treatment, to avoid any sponsor bias (the decision to initiate canakinumab treatment was recorded, however). Therefore, treatment response analysis in this study does not include responses for patients treated with canakinumab.

Outcomes. Patient demographics, genetic data, and clinical characteristics at disease onset, diagnosis, and during treatment were collected. These included treatment duration, reason for discontinuation, functional status improvement, and clinical and biochemical response outcomes. Complete clinical response was defined by a normalization of the associated disease-related symptoms, whereas biochemical control referred to normal levels of CRP/SAA (median <10 mg/liter).

Statistical analysis. Patient characteristics and treatment information were summarized descriptively. Chi-square tests for independence were used to assess potential differences between best clinical and biochemical response rates between biologic agents. All analyses were conducted using SPSS software, version 19.

RESULTS

Physicians from 16 medical centers extracted information relating to 134 patients: FMF (n = 49), TRAPS (n = 47), and MKD/HIDS (n = 38) (for country breakdown, see

Table 2. Referral patterns at time of visit to specialist by patient age*

	FMF†		TRAPS R92Q‡		TRAPS‡		MKD/HIDS‡	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults
No. of patients	36 (73)	13 (27)	4 (67)	2 (33)	17 (41)	24 (59)	25 (66)	13 (34)
No. of physicians seen for PFS before diagnosis								
1–2	30 (83)	8 (62)	–	1 (50)	11 (65)	7 (29)	19 (76)	1 (8)
3–4	5 (14)	4 (31)	3 (75)	–	5 (29)	11 (46)	6 (24)	7 (54)
5–6	1 (3)	1 (8)	–	1 (50)	1 (6)	6 (25)	–	5 (38)
>6	–	–	1 (25)	–	–	–	–	–
Specialty of referring physician§								
General practitioner	7 (21)	6 (46)	1 (25)	–	2 (12)	3 (15)	3 (13)	2 (15)
Pediatrician	19 (58)	2 (15)	2 (50)	–	10 (59)	–	11 (48)	1 (8)
Pediatric rheumatologist	–	1 (8)	–	–	1 (6)	–	2 (9)	–
Rheumatologist	5 (15)	1 (8)	–	–	3 (18)	4 (20)	1 (4)	4 (31)
Other¶	2 (6)	3 (23)	1 (25)	2 (100)	1 (6)	13 (65)	6 (26)	6 (46)
Referring physician diagnosis#								
Correct diagnosis	11 (52)	3 (75)	–	–	1 (11)	5 (28)	3 (23)	–
Incorrect diagnosis								
Incorrect PFS	–	–	–	–	1 (11)	1 (6)	1 (8)	–
PFAPA syndrome	–	–	–	–	1 (11)	–	–	–
JIA	1 (5)	–	–	–	–	–	–	–
Rheumatoid arthritis	–	–	–	–	–	1 (6)	–	–
Auto-inflammatory disease not specified	–	–	1 (25)	–	–	1 (6)	–	3 (50)
Other**	5 (24)	–	–	–	4 (44)	4 (24)	4 (31)	–
None	4 (19)	1 (25)	3 (75)	2 (100)	2 (22)	5 (28)	5 (38)	3 (50)

* Values are the number (%). FMF = familial Mediterranean fever; TRAPS = tumor necrosis factor receptor–associated periodic syndrome; MKD = mevalonate kinase deficiency; HIDS = hyperimmunoglobulinemia D syndrome; PFS = periodic fever syndrome; PFAPA = periodic fever, aphthosis, pharyngitis, and adenitis; JIA = juvenile idiopathic arthritis.
† Countries presented in table for FMF cohort: France, Germany, The Netherlands, UK, Israel, and Turkey. Children refer to patients ages <18 years when first seen by specialist; adults were ages ≥18 years.
‡ Countries presented in table for TRAPS and MKD/HIDS cohorts: US, France, Germany, The Netherlands, UK, Israel, and Turkey. Children refer to patients ages <18 years when first seen by specialist; adults were ages ≥18 years.
§ Referring physician was not indicated on 9 patient records.
¶ Other physicians include cardiologist, infectious disease specialist, immunologist, gastroenterologist, amyloidosis specialist, ear/nose/throat, general surgeon, pediatric surgeon, nephrologist, neurologist, pulmonologist, and internist.
# Referring physician diagnosis available in 79 patient records.
** Other diagnoses include polymyalgia rheumatica, acute rheumatic fever, chronic auto-inflammatory syndrome, Henoch-Schonlein purpura, immune deficiency, inflammatory bowel disease, periodic fever, recurrent idiopathic pericarditis, recurrent Kawasaki disease, septic arthritis, serositis, systemic vasculitis, "ununderstood" inflammation, and urinary tract infection.

Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23120/abstract). Post hoc, 5 FMF patients were excluded because they lacked 2 pathogenic mutations (they were R202Q heterozygous, K695R heterozygous, and E148Q homozygous). Six TRAPS patients with the R92Q mutation were analyzed separately due to previously reported differences in phenotype (Table 1) (7).

FMF. The median age of disease onset and diagnosis of FMF patients who were eligible or treated with biologic agents was 2.0 and 4.9 years, respectively, with a median delay in diagnosis of 1.9 years. Fever and arthritic flares occurred at a median frequency of 26.0 and 12.0 times per year, respectively, with a duration of 3.0 days per attack. The majority of patients (53%) experienced severe serositis (Table 1).

Of the 49 patients with FMF included in the analysis, 73% were ages <18 years when first seen by a specialist. Regardless of age, the majority of patients saw 1 to 2 physicians prior to diagnosis (83% and 62% for children and adults, respectively). Children were primarily diagnosed by pediatricians, whereas adults were mostly seen by general practitioners. The referring physicians were generally accurate with diagnoses, with 52% of children and 75% of adults being correctly diagnosed with FMF (Table 2).

Of the 27 FMF patients exposed to biologic therapy, 82% were provided with an anti–interleukin-1 (anti-IL-1) agent, either anakinra (n = 14) or canakinumab (n = 8), as the first biologic agent. Complete clinical response of patients treated with anakinra was achieved in 7 of 14 cases, whereas biochemical control was achieved in 6 of the 14 cases reviewed. The remaining patients received either an anti–tumor necrosis factor (anti-TNF) (etanercept or adalimumab; n = 4) or interferon-α (n = 1). In patients who received an anti-TNF biologic agent, 25% had complete clinical and biochemical control, although the difference compared to the anti-IL-1 anakinra-treated group was not statistically significant ($P = 0.79$ and $P = 0.42$, respectively). Overall, the mean duration of therapy for anti-IL-1 was 9.7 months compared

Table 3. Summary of usage of biologic agents by line of therapy and disease*

	Patients receiving biologic agents, no.	Anti-IL-1		Anti-TNF		Anti-IL-6: tocilizumab	Other: interferon-α
		anakinra	canakinumab	adalimumab	etanercept		
First biologic agent							
FMF†	27	14 (52)	8 (30)	2 (7)	2 (7)	–	1 (4)
TRAPS R92Q‡	6	2 (33)	–	–	4 (67)	–	–
TRAPS‡	37	15 (41)	2 (5)	–	20 (54)	–	–
MKD/HIDS‡	31	21 (68)	1 (3)	–	8 (26)	1 (3)	–
Second biologic agent							
FMF†	11	6 (55)	5 (45)	–	–	–	–
TRAPS R92Q‡	–	–	–	–	–	–	–
TRAPS‡	12	9 (75)	2 (17)	1 (8)	–	–	–
MKD/HIDS‡	7	1 (14)	3 (43)	–	2 (29)	1 (14)	–
Third biologic agent							
FMF†	–	–	–	–	–	–	–
TRAPS R92Q‡	–	–	–	–	–	–	–
TRAPS‡	4	1 (25)	2 (50)	–	–	1 (25)	–
MKD/HIDS§	2	1 (50)	–	–	–	1 (50)	–

* Values are the number (%) unless indicated otherwise. Treatment patterns are represented by each patient's line of therapy as indicated in each patient's treatment flowchart. Anti-IL-1 = anti–interleukin-1; anti-TNF = anti–tumor necrosis factor; anti-IL-6 = anti–interleukin-6; FMF = familial Mediterranean fever; TRAPS = tumor necrosis factor receptor–associated periodic syndrome; MKD = mevalonate kinase deficiency; HIDS = hyperimmunoglobulinemia D syndrome.
† Countries presented in table for FMF cohort: France, Germany, The Netherlands, UK, Israel, and Turkey.
‡ Countries presented in table for TRAPS and MKD/HIDS cohorts: US, France, Germany, The Netherlands, UK, Israel, and Turkey.
§ Countries presented in table for TRAPS and MKD/HIDS cohorts: US, France, Germany, The Netherlands, UK, Israel, and Turkey. One MKD/HIDS patient was taking a fourth agent, anti-IL-1 (canakinumab).

to 9.3 and 17.0 months for anti-TNF and interferon-α therapy, respectively (Table 3 and Table 4). The 3 patients using anti-TNF and 1 patient using interferon-α therapy discontinued for lack of efficacy. Of the 10 patients discontinuing anakinra treatment, the main reasons cited were side effects (n = 5) and lack of efficacy (n = 4), of which 1 patient experienced both.

TRAPS. Of the 47 TRAPS patients included in the chart review, 6 had the low penetrance R92Q mutation, while the remaining 41 had other mutations. The median age of disease onset and diagnosis for the TRAPS R92Q cohort was 10.4 and 10.9 years, respectively, with a delay in diagnosis of 1.4 years. The TRAPS non-R92Q group (referred to as the TRAPS cohort from hereon) disease onset, diagnosis, and delay had medians of 7.4, 27.6, and 5.8 years, respectively.

The age of patients at the time of data collection was broadly similar for both TRAPS cohorts, although children accounted for 67% of TRAPS R92Q patients and 41% of non-R92Q–mutated patients. Differences between physicians were seen across cohorts and age ranges, with TRAPS R92Q children mostly seeing 3 or 4 physicians prior to diagnosis. Prior to diagnosis, 65% of the TRAPS cohort children saw 1 or 2 physicians, and 46% of adults saw 3 or 4. The referring physician for children was a pediatrician in 2 of 4 R92Q patients and in 10 of 17 TRAPS patients (59%). No diagnosis was provided by the referring physician in the majority of cases (Table 2).

In the TRAPS R92Q cohort, 4 patients were exposed to etanercept as the first biologic agent, and 2 received anakinra. Complete clinical and biochemical responses were achieved in 1 of 4 etanercept patients and in 1 of 2 anakinra patients (Table 3). Of the 41 TRAPS patients, approximately half (54%) were treated with etanercept as the first biologic agent, with the remaining patients being treated with anakinra (41%) and canakinumab (5%). Patients treated with anakinra were significantly more likely to have a complete clinical and biochemical response ($P = 0.03$ and $P < 0.01$, respectively) compared to those treated with anti-TNF. Patients requiring second-line therapy were exposed to anakinra (75%), canakinumab (17%), or adalimumab (8%). Third-line therapies were also focused on anti-IL-1 therapies (75%) (Table 3 and Table 4).

A total of 13 TRAPS patients discontinued anti-TNF treatment, with 1 patient discontinuing both etanercept and adalimumab. Notably, 7 of 13 patients receiving etanercept discontinued due to a lack of efficacy, and 2 of 13 discontinued because they experienced diminished symptoms. Only 6 TRAPS patients receiving anakinra discontinued this therapy, with the main reasons being side effects (n = 2) and enrollment in a clinical trial (n = 2).

MKD/HIDS. MKD/HIDS patients had a median age of disease onset and diagnosis of 0.5 and 8.9 years, respectively, with a median delay in diagnosis of 7.1 years. Fever and arthritic flares occurred at a median frequency of 12.0 and 12.5 times per year, respectively, with a duration of 5.0 and 7.5 days per attack. The majority of patients experienced severe cases of fever (87%) or elevated acute-phase reactants (79%), and most of the time these events occurred together (74%) (Table 1). Over half of the patients experienced painful lymph nodes, loss of appetite, nausea, abdominal pain, diarrhea, or oral ulcers. None of the more severe phenotypes involving neurologic complications (typically grouped under the diagnosis of mevalonic aciduria) were noted in this patient cohort.

Table 4. Summary of complete response rates of biologic agents by disease*

Disease and agent	Overall		First agent				Second agent			
	Patients exposed	Duration: mean, median (range), months	Patients exposed	Complete clinical response†	Complete biochemical response†	Functional status improved‡	Patients exposed	Complete clinical response†	Complete biochemical response†	Functional status improved‡
FMF§										
Anti-IL-1	33 (87)	9.7, 3.0 (1.0–96.0)	22 (82)	7 (50)	6 (43)	10 (91)	11 (100)	1 (33)	1 (33)	1 (50)
Anti-TNF	4 (11)	9.3, 8.0 (3.0–18.0)	4 (15)	1 (25)	1 (25)	1 (33)	–	–	–	–
IFNα	1 (3)	17.0, 17.0 (17.0–17.0)	1 (4)	–	–	–	–	–	–	–
TRAPS R92Q¶										
Anti-IL-1	2 (33)	18.0, 18.0 (6.0–30.0)	2 (33)	1 (50)	1 (50)	1 (100)	–	–	–	–
Anti-TNF	4 (67)	8.8, 6.0 (3.0–20.0)	4 (67)	1 (25)	1 (25)	3 (75)	–	–	–	–
TRAPS¶										
Anti-IL-1	31 (58)	19.8, 10.5 (1.0–108.0)	17 (46)	14 (93)#	15 (100)**	12 (80)	11 (92)	4 (44)	6 (67)	6 (75)
Anti-TNF	21 (40)	25.4, 14.0 (1.0–84.0)	20 (54)	12 (60)#	8 (40)**	6 (43)	1 (8)	–	–	1 (100)
Anti-IL-6	1 (2)	16.0, 16.0 (16.0–16.0)	–	–	–	–	–	–	–	–
MKD/HIDS¶										
Anti-IL-1	28 (68)	19.3, 17.0 (0.2–64.0)	22 (71)	11 (52)	9 (43)	13 (81)	4 (57)	–	–	–
Anti-TNF	10 (24)	29.2, 14.5 (2.0–94.0)	8 (26)	7 (88)	6 (75)	7 (100)	2 (29)	–	–	0 (0)
Anti-IL-6	3 (7)	6.0, 3.0 (3.0–12.0)	1 (3)	1 (100)	1 (100)	1 (100)	1 (14)	–	–	–

* Values are the number (%) unless indicated otherwise. Anti–interleukin-1 (anti-IL-1) agents anakinra and canakinumab; anti–tumor necrosis factor (anti-TNF) agents adalimumab and etanercept; and anti-IL-6 agent tocilizumab. Clinical and biochemical response was defined based on the best response across each course of treatment. Complete clinical response: no disease-associated symptoms; complete biochemical response: normal levels of C-reactive protein/serum amyloid A protein (median <10 mg/liter). FMF = familial Mediterranean fever; IFNα = interferon-α; TRAPS = tumor necrosis factor receptor–associated periodic syndrome; MKD = mevalonate kinase deficiency; HIDS = hyperimmunoglobulinemia D syndrome.

† Canakinumab response data were not collected as per exclusion criteria.

‡ Functional status improvement rated on 1–5 scale at end of treatment or last followup by the treating physician, where 1 = minor improvement and 5 = marketed improvement. Analysis of 4s and 5s for known scores only.

§ Countries presented in table for FMF cohort: France, Germany, The Netherlands, UK, Israel, and Turkey.

¶ Countries presented in table for TRAPS and MKD/HIDS cohorts: US, France, Germany, The Netherlands, UK, Israel, and Turkey.

Difference in clinical response for anakinra and anti-TNF agents was statistically significant in TRAPS patients ($P = 0.03$).

** Difference in biochemical response for anakinra and anti-TNF agents was statistically significant in TRAPS patients ($P < 0.01$).

Of the 38 patients with MKD/HIDS, 66% were ages <18 years when they were first seen by a specialist. Children were primarily seen by 1 to 2 physicians (76%), whereas adults predominantly saw >3 physicians before diagnosis (92%). Similar to the other periodic fevers, children were generally referred by pediatricians (57%). Diagnosis was either not reported, or was incorrect, in 77% of children at the time of referral to a specialist, whereas adults were seen by a variety of specialists, none of whom correctly diagnosed the patient (Table 2).

In MKD/HIDS patients receiving biologic therapy, 71% received anti-IL-1 as their first agent, with 68% receiving anakinra. Anti-TNF (etanercept) and anti-IL-6 (tocilizumab) were given to 26% and 3% of patients, respectively. The differences in complete clinical response between anakinra and etanercept (52% versus 88%) did not reach statistical significance ($P = 0.08$ for clinical control and $P = 0.12$ for biochemical control). Canakinumab was mainly used as a second biologic agent in 3 of 7 cases, with limited use of etanercept (2 of 7), anakinra (1 of 7), and tocilizumab (1 of 7) (Table 3 and Table 4).

Biologic treatment was discontinued in 15 patients. Lack of efficacy was the reason for discontinuation for all 4 patients receiving etanercept and for the patient taking tocilizumab. Of the 10 anakinra patients who stopped treatment, lack of efficacy (n = 5) and patient's wish/preference (n = 3) were the most common reasons.

Mutations. All patient cases in this study were diagnosed via clinical testing. In addition, all patient cases reported a mutation. At the time of referral to a PFS specialist, 71% of FMF, 79% of TRAPS, and 63% of MKD/HIDS patients underwent genetic testing. The majority of FMF patients (90%) had the M694V point-mutation in the *MEFV* gene, mostly homozygous in nature (84%) (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23120/abstract). In the TRAPS cohort, there was a greater variety of mutations seen within the *TNFRSF1A* gene, with 17% involving cysteine mutations; 17% were T50M mutations (see Supplementary Table 3). Lastly, the majority of patients with MKD/HIDS (82%) carried the common V377I mutation in the *MVK* gene and were mostly compound heterozygous with a variety of other mutations (81%) (see Supplementary Table 4).

DISCUSSION

This article describes one of the largest, and most geographically dispersed, retrospective analyses of clinically diagnosed PFS patients who are currently being treated for FMF, TRAPS, or MKD/HIDS. Participating physicians were internationally recognized specialists in treating these conditions.

As expected, a high proportion of these biologic agent–eligible or treated patients across all 3 conditions had severe fever symptoms at disease onset. In addition, the FMF cohort had the highest rate of severe serositis (53%). In TRAPS and MKD/HIDS, elevated acute-phase reactants and GI upset were the most common symptoms classed as severe. The likelihood of correct diagnosis and associated referral patterns were correlated with the frequency of disease incidence. A long delay from disease onset to diagnosis was seen within TRAPS and MKD/HIDS (5.8 and 7.1 years, respectively) compared to 1.8 years in the FMF cohort. Treatment patterns largely followed previous guidelines. An approximately equal proportion of TRAPS patients received anti-IL-1 and anti-TNF biologic agents in first-line, whereas IL-1 blockade was the main choice for FMF and MKD/HIDS patients.

The FMF patients included in this study notably had unusually severe forms of the disease, with an inadequate response to colchicine, and only represent a very small portion of the FMF population (8). Unfortunately no definition of colchicine resistance/intolerance has been widely agreed upon (9–12). However, the definition for this study is in accordance with multiple articles that have specifically addressed this issue (13,14).

This study found differences between adults and children, and also between TRAPS and MKD/HIDS patients, in referral patterns. The majority of FMF children (83%) were only seen by 1 or 2 physicians before they were referred to a recognized expert. The percentage of patients seen by >3 physicians before referral was much lower in children than in adults. This finding suggests that physicians treating difficult FMF refer children more quickly to specialists than adults are referred. Alternatively, the finding might mean patients diagnosed in adulthood have had their diagnosis missed by multiple physicians.

Furthermore, 15% of adult FMF patients were referred by a pediatrician. This fact reflects the transition of patients from pediatricians upon reaching adulthood and the increased disease awareness among pediatricians. The recommendations by pediatricians may also suggest that pediatricians refer previously undiagnosed parents or older siblings. In this study, a large portion of the FMF patients (65%) were from Turkey and Israel, where the disease is frequent and well recognized (15–17). This fact may explain the moderately higher percentage of patients correctly diagnosed by referring physicians in Turkey and Israel (56%) compared with Europe (40%). There are regions in Europe, however, where physicians have good awareness of FMF due to the higher numbers of residents with the relevant ethnic background.

The majority of the FMF patients who had an inadequate response to colchicine went on to receive biologic treatments. The most common biologic agent was anti-IL-1 therapy, to which 50% of patients responded. There are differences between the mean (9.3 months) and median (3.0 months) duration of anti-IL-1 therapies, suggesting specialist physicians may use these agents on demand or short-term for control.

In the anti-TNF–treated FMF group (n = 4), there was a 25% clinical and biochemical response rate observed. However, this result should be interpreted with caution due to the limited number of patients. Of these patients, 2 had sacroiliitis, with both experiencing at least a partial response, confirming that anti-TNF may be effective for this feature of the disease.

TRAPS is a rare disease whose diagnosis relies on a high index of suspicion; consequently, there is a need for

physician awareness (18). In this study, TRAPS patients saw more physicians before a correct diagnosis (median 3.0) than FMF patients (median 2.0), and were rarely diagnosed correctly before referral to a specialist. As only 6 TRAPS patients carrying the R92Q mutation were included in the study, interpretation is difficult, but we confirm from previously published evidence that these patients have a similar phenotype as patients with other *TNFRSF1A* mutations, but with shorter and more frequent disease flares. Furthermore, patients with the R92Q mutation had a shorter delay, and lower age, in diagnosis (5.8 and 16.7 years, respectively); the reason for this finding is unclear but may be due to the small patient numbers. R92Q TRAPS is less frequently associated with a family history, so the finding is unlikely to reflect family screening.

Approximately equal numbers of TRAPS patients in this study received anti-IL-1 and anti-TNF as first-line biologic treatment. We observed a significantly better clinical and biochemical response rate to anti-IL-1 treatment compared with anti-TNF agents. Of the 20 TRAPS patients receiving anti-TNF therapy as a first-choice biologic agent, 13 discontinued, including 7 of 12 who at some point in their treatment had complete clinical control, and 5 of 8 who had complete biochemical control. Reasons for discontinuing anti-TNF treatment ranged from apparent disease amelioration over time to lack of efficacy. Anti-TNF agents may be given as a monotherapy or with methotrexate in an effort to block antibody production and control symptoms in the longer term. However, the 65% discontinuation rate is consistent with a previous retrospective analysis of this patient population describing low and transient response rates in TRAPS patients treated with anti-TNF therapies (19). Based on findings from this study and existing published evidence, we recommend the use of anti-IL-1 agents as the first biologic treatment.

MKD/HIDS is the rarest of the 3 PFS conditions described in this study (5,20,21), and the collection of longitudinal records of 38 patients represents an important data set. Of the PFS conditions observed, MKD/HIDS has the earliest disease onset (median of 0.5 years). The low awareness for this disease is reflected by the lack of diagnosis until approximately age 9 years, a 7-year delay in diagnosis from symptom onset, and patients being seen by nearly 3 physicians before referral to a recognized fever syndrome specialist. In addition, adult rheumatologists are even less familiar with these diseases, which can lead to further delays in diagnosis. A clear diagnostic guideline is therefore a critical need.

MKD/HIDS patients may have several phenotypes, and single cases of early-onset inflammatory bowel disease and hepatosplenomegaly were reported in this chart review. Current treatment has been focused on using anti-IL-1 (71% in first-line), particularly anakinra, likely due to a previous prospective study showing favorable efficacy (22). Despite the majority of MKD/HIDS patients in this small study receiving anti-IL-1, there were no clear differences in response compared to anti-TNF, consistent with previous real-world data suggesting that there is no current evidence to support any particular order of biologic treatment options (6). A limitation of this study may be that no separate analysis could be performed for continuous versus intermittent use of biologic agents. This distinction may be especially important in MKD/HIDS, where anakinra has been used to abort inflammatory attacks. Additionally, 1 potential source of bias is that differences observed between treatments could be due to differences in treating centers and their specific patient populations. We found there was a preference for 1 type of biologic agent in the majority of centers, with only 25% of centers (4 of 16) using multiple agents in the first-line setting. As this study focused on real-world treatment patterns, we did not design the study to control for this potential bias.

This retrospective study highlights the unmet needs for the management of patients with FMF, TRAPS, and MKD/HIDS. Referral patterns to specialized centers were assessed showing the impact of disease rarity on nondiagnosis or misdiagnosis and diagnostic delay. We note the need for greater awareness of these diseases and the importance of improved diagnostics, particularly among the adult population.

Biologic therapies have been widely adopted to treat otherwise inadequately controlled disease. This comparative assessment of real-world treatment response for current therapies will support further refinement of optimal treatment practice of these PFS conditions. A limitation of the study is the lack of independent measures to quantify treatment efficacy. Therefore, further prospective studies and randomized trials that include robust measures of disease outcomes are needed to determine the most appropriate treatment options for these patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ozen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE STUDY SPONSOR

Novartis participated in study design, operational execution, biostatistical analysis, and drafting of the article through Navigant Consulting. The decision to submit the manuscript for publication was left up to the authors. All authors approved the publication for submission.

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