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International retrospective chart review of treatment patterns in severe FMF, TRAPS and MKD/HIDS

Running headline: Real world experience in three periodic fever syndromes

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ABSTRACT

Objectives: Periodic fever syndromes (PFS) are characterised by recurrent attacks of fever and localised inflammation. This study examined the diagnostic pathway and treatments at tertiary centres for FMF, TRAPS and MKD/HIDS.

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

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

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

Significance and Innovations

- This study is one of the largest retrospective analyses of biological eligible/currently treated patients with the periodic fever syndromes of FMF, TRAPS and MKD/HIDS in geographic scope, patient recruitment and medical centre participation
- A long delay from disease onset to diagnosis was seen within TRAPS and MKD/HIDS (5.8 years and 7.1 years, respectively) with a 1.8-year delay in FMF
- An equal proportion of TRAPS patients first received anti-IL-1 and anti-TNF biologics whereas IL-1 blockade was the main choice for MKD/HIDS and FMF patients
- For TRAPS patients, treatment with anakinra versus anti-TNF treatments as first biologic resulted in significantly higher clinical and biochemical responses ($p=0.03$ and $p<0.01$, respectively). Therefore, the authors would recommend use of IL-1 inhibition over TNF inhibition in TRAPS patients as first biologic agent based on findings from this study and other existing literature. No significant differences in responses were observed between biological agents among other cohorts

INTRODUCTION

Periodic fever syndromes (PFS) are characterised by attacks of clinical and biochemical inflammation. They are often associated with genetic defects in the innate immune system and a chronic disease course; the patients may suffer from the sequelae of persistent inflammation.[1, 2] The three best known PFSs are the scope of the present study: Familial Mediterranean Fever (FMF), Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and Mevalonate Kinase Deficiency (MKD) associated periodic syndrome, also known as hyper-immunoglobulinemia D syndrome (HIDS). Although they have different clinical features and etiology, all three are characterised by intermittent attacks, fever and high acute phase reactants.[3] With the exception of the eastern Mediterranean, each has a very low prevalence[4, 5] and thus are considered rare diseases. Recent recommendations from Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) have focused on the clinical management of TRAPS, MKD/HIDS and cryopyrin-associated periodic syndromes, but have referenced a lack of evidence of patient treatment experience and outcomes.[6] This international study was designed to analyse real-life data to describe diagnostic pathway, referral to tertiary centres and subsequent treatment by specialists.

METHODS

Data source

Medical centres in the USA, European Union (France, Germany, Italy, the Netherlands and the United Kingdom) and Eastern Mediterranean (Israel and Turkey) which specialised 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 (IRB)/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 who met all the following inclusion criteria were considered for enrolment: 1) children or adults who have clinically and/or genetically confirmed diagnosis of FMF, TRAPS or MKD/HIDS; 2) were treated by a specialist physician for the relevant disease at any point during the period between 2008 and 2012 with a minimum length of follow up after diagnosis of 12 months; and 3) are either eligible for or receiving treatment with a biologic therapy.

Specific criteria defined inadequate disease control for FMF, TRAPS and MKD/HIDS thereby suggesting patients eligible for a biologic.

For FMF, patients were required to have an inadequate response to colchicine, defined as either a minimum of one typical acute attack per month for at least three consecutive months or continued attacks in a patient compliant with or intolerant to effective doses of colchicine. For TRAPS, patients were required to show inadequate disease control with corticosteroids prior to receiving an effective biologic therapy, defined as more than six episodes per year or elevated C-reactive protein (CRP) >10mg/L and/or serum amyloid A protein (SAA) >10 mg/L between attacks. Lastly, for MKD/HIDS, inadequate control 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 >10mg/L and/or

SAA >10 mg/L in between attacks. On-treatment efficacy and duration data was not collected for patients enrolled into an interventional clinical study or following initiation of canakinumab treatment to avoid any sponsor bias (the decision to initiate of canakinumab was however recorded). 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 including treatment duration, reason for discontinuation, functional status improvement, clinical and biochemical response outcomes. Complete clinical response was defined by a normalisation of the associated disease-related symptoms, whereas biological control referred to normal levels of CRP / SAA (median <10mg/L).

Statistical analyses

Patient characteristics and treatment information were analysed descriptively. Chi-square test for independence was used to assess differences between best clinical and biochemical response rates between biologic agents. All analyses were conducted using IBM SPSS Statistics 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp).

RESULTS

Physicians from 16 medical centres extracted information on 134 patients: FMF (n=49), TRAPS (n=47), and MKD/HIDS (n=38; see Supplemental Table S1 for country breakdown). Post-hoc,

five FMF patients were excluded because they lacked two pathogenic mutations (they were R202Q heterozygous, K695R heterozygous and E148Q homozygous).

Six TRAPS patients with the R92Q mutation were analysed separately due to previously reported differences in phenotype (Table 1).[7]

FMF

The median age of disease onset and diagnosis of these biological eligible/treated FMF patients 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 (53%) of patients experienced severe serositis (Table 1).

Of the 49 patients with FMF included in the analysis, 73% were less than 18 years old when first seen by a specialist. Regardless of age, the majority saw between 1-2 physicians prior to diagnosis (83% and 62% for children and adults, respectively). The children were primarily diagnosed by paediatricians whereas adults were mostly seen by general practitioners. The referring physician diagnosis was mostly accurate, with 52% of children and 75% of adults correctly diagnosed with FMF by the referring physician (Table 2).

Of the 27 FMF patients exposed to biologic therapy, 82% were provided an anti-IL-1 agent, either anakinra (14) or canakinumab (8), as the first biologic. Complete clinical response of patients treated with anakinra was achieved in 7 out of 14 cases whereas biological control was achieved in 6 out of 14 cases reviewed. The remaining patients received either an anti-TNF (etanercept or adalimumab; 4) or interferon alpha (1). 25% of patients who received a non-IL-1

biologic had complete clinical and biological control, although the difference compared to the anti-IL-1 anakinra treated group was not statistically significant ($p = 0.79$ and $p = 0.42$). Overall, the mean duration of therapy for anti-IL-1 was 9.7 months compared to 9.3 and 17.0 months for anti-TNF and interferon alpha therapy (Table 3, Table 4).

Lack of efficacy was the reason for discontinuation for all 3 patients on anti-TNF therapy and 1 patient on interferon therapy. Of the 10 patients discontinuing anakinra treatment, the main reasons cited were side effects (5) and lack of efficacy (4), of which 1 patient experienced both.

TRAPS

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

The age of patients at time of data collection was broadly similar for both TRAPS cohorts, although children accounted for 67% of TRAPS R92Q and 41% of non-R92Q mutations. Differences existed in physicians seen across cohorts and age ranges, with TRAPS R92Q children mostly seeing 3-4 physicians prior to diagnosis (3 of 4). For the TRAPS cohort, 65% of children saw 1-2 physicians and 46% of adults saw 3-4 pre-diagnosis. The referring physician of children was a paediatrician in 2 of 4 and 10 of 17 (59%) cases for the R92Q and TRAPS population respectively. In the majority of cases, no diagnosis was provided by the referring physician (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 in 4 (25%) etanercept patients and 1 of 2 (50%) anakinra patients (Table 3).

Of the 41 TRAPS patients, approximately half of the patients were treated with etanercept as first biologic (54%) with the remaining patients being treated with anakinra (41%) and canakinumab (5%). Patients were significantly more likely to have a complete clinical response ($p = 0.03$) and complete biochemical response ($p < 0.01$) on anakinra compared to 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, Table 4).

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 lack of efficacy and 2 due to diminished symptoms. Only 6 TRAPS patients receiving anakinra discontinued this therapy with the main reasons being side effects (2) and enrolment in a clinical trial (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 with a duration of 5.0 and 7.5 days per attack, respectively. The majority of patients experienced severe cases of fever (87%) or elevated acute phase reactants (79%), most of the time together (74%; Table 1). Over half of patients suffered from painful lymph nodes, loss of appetite, nausea, abdominal pain, diarrhoea and oral ulcers.

None of the more severe phenotypes involving neurological complications (and typically grouped under the diagnosis of mevalonic aciduria) were noted in this patient cohort.

Of the 38 patients with MKD/HIDS, 66% were less than 18 years old when first seen by a specialist. Children were primarily seen by 1-2 physicians (76%) whereas adults mostly saw more than three physicians before diagnosis (92%). Similar to the other periodic fevers, children were generally referred by paediatricians (57%). Incorrect or no diagnosis was reported for 77% of children at the time of referral to a specialist, whereas adults were seen by a variety of specialties, none of whom produced a correct diagnosis (Table 2).

For MKD/HIDS patients receiving biologic therapy, 71% received anti-IL-1 as a first agent, 68% being anakinra. Anti-TNF (etanercept) and anti-IL6 (tocilizumab) were given to 26% and 3% of patients, respectively. The differences in complete clinical response between anakinra and anti-TNF (52% vs. 88%) did not reach statistical significance ($p = 0.08$ and $p = 0.12$ for clinical and biologic control, respectively). A similar non-significant difference was found for complete biochemical response (43% vs. 75% for anti-IL-1 and anti-TNF). 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, Table 4).

15 patients discontinued biologic treatment. All 4 etanercept and 1 tocilizumab discontinuations were for lack of efficacy. Of the 10 anakinra patients stopping treatment, 5 were due to lack of efficacy and 3 because of patient's wish/preference.

Mutations

All patient cases in this study were diagnosed on clinical grounds. In addition, all patient cases in this study reported a mutation. At 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%; Supplemental Table S2).

There was a greater variety of TRAPS mutations seen to the *TNFRSF1A* gene, with 17% involving cysteine mutations; 17% were T50M mutations (Supplemental Table S3).

The majority of patients with MKD/HIDS (82%) carried the common V377I mutation, and were mostly compound heterozygous with a variety of other mutations (81%; Supplemental Table S4).

DISCUSSION

This study represents one of the largest retrospective analyses of biological eligible/currently treated patients with the periodic fever syndromes, FMF, TRAPS and MKD/HIDS in geographic scope, patient recruitment and medical centre participation. Participating physicians were internationally recognised specialists in treating these conditions.

As expected, a high proportion of these biological eligible/treated patients across all three conditions presented at disease onset with severe fever symptoms. 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 frequency of disease

incidence. A long delay from disease onset to diagnosis was seen within TRAPS and MKD/HIDS (5.8 years 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 biologics in first line whereas IL-1 blockade was the main choice for MKD/HIDS and FMF patients.

FMF

It should be underlined that the FMF patients analysed had unusually severe 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 papers that have specifically addressed this issue.[13, 14]

In this study there were differences in referral to the specialist not only between adults and children but also compared to TRAPS and MKD/HIDS. The majority of the childhood FMF patients (83%) were seen only by 1-2 physicians before they were referred to a recognised expert. The percentage of patients seen by >3 physicians were much less in children than adults. This suggests that physicians treating difficult paediatric FMF refer more quickly to specialists than do physicians treating difficult FMF in adults. Alternatively, this might simply reflect that patients diagnosed in adulthood had lived long enough to have their diagnosis missed by multiple physicians.

Furthermore, it is interesting to note that 15% of adult FMF patients were referred by a paediatrician. This reflects transition of patients from paediatricians upon reaching adulthood and the disease awareness among paediatricians and suggests they are likely refer the previously

undiagnosed parents or older siblings to specialists as well. In this study a large portion of the FMF patients (65%) were from Turkey and Israel where the disease is frequent and well recognised.[15-17] This may explain the moderately higher percentage of patients correctly diagnosed by referring physician between Turkey and Israel (56%) and Europe (40%). Although, it should be noted that there are regions in Europe 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 of which anti-IL-1 treatments were the most common and 50% of the patients responded to anti-IL-1 treatment. It is also noted that 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 biologic response rate observed. However, this result should be interpreted with caution due to the limited patient numbers. Of these patients, two had sacroiliitis, with both experiencing at least a partial response, confirming that anti-TNF may be effective for this feature of the disease.

TRAPS

TRAPS is a rare disease whose diagnosis relies on a high index of suspicion, consequently there is a need for physician awareness.[18, 19] In this study TRAPS patients saw more physicians before a correct diagnosis (median of 3.0) than FMF (median of 2.0) and are rarely diagnosed correctly before referral to a specialist. Inclusion of only six R92Q patients means interpretation is difficult, but we confirm previous published evidence that these patients have a similar phenotype as patients with other *TNFRSF1A* mutations but with shorter and more frequent

disease flares. Furthermore, the R92Q population had a shorter delay in diagnosis (5.8 years) and lower age at diagnosis (16.7 years); the reason for this is unclear; it may be an artefact of small patient numbers. R92Q TRAPS is less frequently associated with a family history so this is unlikely to reflect family screening.

Of the TRAPS patients in this study who were not able to achieve control without biologic treatment, almost equal numbers received IL-1 targeting treatment and anti-TNF treatment as first-line biologic treatment. We observed a significantly better biologic and clinical response rate to anti-IL-1 treatment compared with anti-TNF agents. Of the 20 TRAPS patients receiving anti-TNF therapy as first choice biologic, 13 discontinued the anti-TNF, including 7 of 12 who at one point in their treatment had complete clinical control, and 5 of 8 who had complete biochemical control. Reasons for discontinuation of anti-TNF treatment range from apparent disease amelioration over time to lack of efficacy. It is noted that 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.[20] Based on findings from this study and existing literature, the authors would recommend use of anti-IL-1 agents first line as the most effective class of biologics for TRAPS.

MKD/HIDS

MKD/HIDS is the rarest of the three PFSs described in this study,[5, 21, 22] and the collection of longitudinal records of 38 patients represents an important dataset. It has earliest onset (median of 0.5 years). The low awareness for this disease is reflected by the lack of diagnosis until

approximately 9 years of age, a 7-year delay in diagnosis from symptom onset, and a mean of 2.8 physicians seen before referral to a recognised fever syndrome specialist. In addition, adult rheumatologists are even less familiar with these diseases and this can also lead to delays in diagnosis. A clear diagnostic guideline is therefore a critical need.

It is noted that MKD/HIDS patients may have several phenotypes and single cases of early-onset inflammatory bowel disease and hepatosplenomegaly reported in this case review. Treatment has been focused on using anti-IL-1 (71% in first line), particularly anakinra, likely due to a prospective study showing favourable efficacy.[23] Despite the majority of MKD/HIDS patients in this small retrospective study receiving anti-IL-1, there were no clear differences in response compared to anti-TNF, consistent with previous real world data suggesting 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 biologicals. This may be especially important in MKD/HIDS where anakinra has been used to abort inflammatory attacks. Additionally, one potential source of bias is that differences observed between treatments could be due to differences in treating centres and their specific patient populations. We found there was a preference for one type of biologic agent in the majority of centres with only 25% of centres (4 of 16) using multiple agents in first line setting. As this study focussed on real world treatment patterns, we did not design this study to control for this potential bias.

Conclusions

This retrospective study highlights unmet needs for management of patients with FMF, TRAPS or MKD/HIDS. Referral patterns to specialised centres were assessed showing the impact of

disease rarity on non- or misdiagnosis and diagnostic delay. We note the need for greater awareness and the importance of improved diagnostics, particularly for the adult population.

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

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TABLES

Table 1. Patient clinical characteristics at disease onset and diagnosis

	FMF[1] (n=49)	TRAPS R92Q[2] (n=6)	TRAPS[2] (n=41)	MKD/HIDS[2] (n=38)
Age at disease onset (years), median (range)	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), median (range)	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), median (range)	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 (per annum), median (range), [N]				
Fever attacks[3]	26.0 (4.0 - 60.8) [43]	12.0 (1.0 - 36.5) [5]	6.0 (2.0 - 120.0) [29]	12.0 (4.0 - 36.5) [35]
Arthritic attacks[3]	12.0 (6.0 - 52.0) [19]	12.0 (12.0 - 12.0) [1]	7.3 (3.0 - 12.0) [8]	12.5 (4.0 - 36.5) [8]
Duration of flares at disease onset (days), median (range)				
Fever attacks[3]	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]	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,[4] n (%)				
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[5]	20 (41%)	3 (50%)	22 (54%)	44 (116%)[5]

Notes:

[1] Countries presented in table for FMF cohort: France, Germany, Netherlands, United Kingdom, Israel and Turkey

[2] Countries presented in table for TRAPS and MKD/HIDS cohorts: USA, France, Germany, Netherlands, United Kingdom, Israel and Turkey

[3] Fever and arthritic attacks can occur simultaneously

[4] Severity characterised as response of Severe and Very Severe based on physician characterisation

[5] Multiple options of GI upset could be selected including abdominal pain, loss of appetite, nausea/vomiting and diarrhoea

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

	FMF[1]		TRAPS R92Q[2]		TRAPS[2]		MKD/HIDS[2]	
	Children[3]	Adults[3]	Children[3]	Adults[3]	Children[3]	Adults[3]	Children[3]	Adults[3]
Number of patients, n (%)	36 (73%)	13 (27%)	4 (67%)	2 (33%)	17 (41%)	24 (59%)	25 (66%)	13 (34%)
Number of physicians seen for PFS before diagnosis, n (%)								
[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,[4] n (%)								
General practitioner (GP)	7 (21%)	6 (46%)	1 (25%)	--	2 (12%)	3 (15%)	3 (13%)	2 (15%)
Pediatricians	19 (58%)	2 (15%)	2 (50%)	--	10 (59%)	--	11 (48%)	1 (8%)
Pediatric rheumatologists	--	1 (8%)	--	--	1 (6%)	--	2 (9%)	--
Rheumatologists	5 (15%)	1 (8%)	--	--	3 (18%)	4 (20%)	1 (4%)	4 (31%)
Other[5]	2 (6%)	3 (23%)	1 (25%)	2 (100%)	1 (6%)	13 (65%)	6 (26%)	6 (46%)
Referring physician diagnosis,[6] n (%)								
Correct diagnosis	11 (52%)	3 (75%)	--	--	1 (11%)	5 (28%)	3 (23%)	--
Incorrect diagnosis								
Incorrect PFS	--	--	--	--	1 (11%)	1 (6%)	1 (8%)	--
PFAPA	--	--	--	--	1 (11%)	--	--	--
JIA	1 (5%)	--	--	--	--	--	--	--
Rheumatoid arthritis (RA)	--	--	--	--	--	1 (6%)	--	--
Auto-inflammatory disease not specified	--	--	1 (25%)	--	--	1 (6%)	--	3 (50%)
Other[7]	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%)

Notes:

[1] Countries presented in table for FMF cohort: France, Germany, Netherlands, United Kingdom, Israel and Turkey

[2] Countries presented in table for TRAPS and MKD/HIDS cohorts: USA, France, Germany, Netherlands, United Kingdom, Israel and Turkey

[3] Children refer to patients less than 18 years of age at time when first seen by specialist; adults were 18 years of age or older

[4] Referring physician was not indicated on 9 patient records

[5] Other physicians include cardiologist, infectious disease specialist, immunologist, gastroenterologist, amyloidosis specialist, ENT, general surgeon, paediatric surgeon, nephrologist, neurologist, pulmonologist and internist

[6] Referring physician diagnosis available in 79 patient records

[7] 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

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

	First Biologic Agent						
	Patients who received biologics, n	**Anti-IL-1**		**Anti-TNF**		**Anti-IL-6**	**Other**
		anakinra	canakinumab	adalimumab	etanercept	tocilizumab	interferon alpha
FMF[2]	27	14 (52%)	8 (30%)	2 (7%)	2 (7%)	--	1 (4%)
TRAPS R92Q[3]	6	2 (33%)	--	--	4 (67%)	--	--
TRAPS[3]	37	15 (41%)	2 (5%)	--	20 (54%)	--	--
MKD/HIDS[3]	31	21 (68%)	1 (3%)	--	8 (26%)	1 (3%)	--
	Second Biologic Agent						
FMF[2]	11	6 (55%)	5 (45%)	--	--	--	--
TRAPS R92Q[3]	--	--	--	--	--	--	--
TRAPS[3]	12	9 (75%)	2 (17%)	1 (8%)	--	--	--
MKD/HIDS[3]	7	1 (14%)	3 (43%)	--	2 (29%)	1 (14%)	--
	Third Biologic Agent						
FMF[2]	--	--	--	--	--	--	--
TRAPS R92Q[3]	--	--	--	--	--	--	--
TRAPS[3]	4	1 (25%)	2 (50%)	--	--	1 (25%)	--
MKD/HIDS[3] [4]	2	1 (50%)	--	--	--	1 (50%)	--

Notes:

[1] Treatment patterns are represented by each patient's line of therapy as indicated in each patient's treatment flowchart

[2] Countries presented in table for FMF cohort: France, Germany, Netherlands, United Kingdom, Israel and Turkey

[3] Countries presented in table for TRAPS and MKD/HIDS cohorts: USA, France, Germany, Netherlands, United Kingdom, Israel and Turkey

[4] One MKD/HIDS patient was on a fourth agent anti-IL-1 (canakinumab)

Table 4. Summary of complete response rates of biologic agents by disease[1][2]

Disease	Agent	Overall		First Agent				Second Agent			
		Patients Exposed, n (%)	Duration (Months), Mean, Median (Range)	Patients Exposed, n (%)	Complete Clinical Response, n (%)[3]	Complete Biochemical Response, n (%)[3]	Functional Status Improved, n (%)[4]	Patients Exposed, n (%)	Complete Clinical Response, n (%)[3]	Complete Biochemical Response, n (%)[3]	Functional Status Improved, n (%)[4]
FMF[5]	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%)	--	--	--	--
	Interferon alpha	1 (3%)	17.0, 17.0 (17.0 - 17.0)	1 (4%)	--	--	--	--	--	--	--
TRAPS R92Q[6]	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[6]	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[6]	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%)	--	--	--

Notes:

[1] IL-1 agents: anakinra and canakinumab; anti-TNF agents: adalimumab and etanercept; and IL-6 agents: tocilizumab

[2] Clinical and biochemical response was defined based on the best response across each course of treatment; complete clinical response was defined as no disease-associated symptoms; complete biochemical response was defined as normal levels of CRP / SAA (median <10mg/l)

[3] Canakinumab response data was not collected as per exclusion criteria

[4] Functional status improvement rated at 1-5 scale at end of treatment or last follow up by the treating physician. 1 represents 'minor improvement' to 5 'marketed improvement'. Analysis of 4s and 5s for known scores only.

[5] Countries presented in table for FMF cohort: France, Germany, Netherlands, United Kingdom, Israel and Turkey

[6] Countries presented in table for TRAPS and MKD/HIDS cohorts: USA, France, Germany, Netherlands, United Kingdom, 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 ($p < 0.01$)