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Therapeutic management of idiopathic recurrent serositis: a retrospective study

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Abstract. – OBJECTIVE: Idiopathic recurrent serositis (IRS) is the most frequent serositis encountered in real-life medical sceneries, and its management represents a therapeutic challenge. There are few epidemiologic data related to IRS, though most studies have focused on recurrent pericarditis, revealing that 70% of all forms of pericarditis are idiopathic and caused by innate immunity abnormalities. The aim of this study was to evaluate outcome and recurrence rates of patients with IRS, assessing management modalities used in our Periodic Fever Centre of the Gemelli Hospital, Rome, Italy, in comparison with previous treatments in other centres.

PATIENTS AND METHODS: Retrospectively, we analyzed the medical charts of 57 unselected patients with history of IRS managed during the period 1998-2017.

RESULTS: A strong heterogeneity emerged by evaluating treatments of this cohort. In particular, in our Centre there was a larger use of combined therapies: 14 patients out of 27 (52%) were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine, compared to only 2 patients (7.4%) previously treated with combined treatments. We used corticosteroid monotherapy only in 1 case, against 7 from other centres. The mean duration of NSAID treatment in other hospitals was 43.8 days (SD ±27.40) and 191.25 days (SD ±42.23) in our Centre; the mean duration of corticosteroid treatment in other hospitals was 101.5 days (SD ±56.40) and 180.7 days (SD ±84.87) in our Centre. Colchicine was administered in other hospitals for the same duration of NSAIDs, and corticosteroids with an average duration of 111 days (SD ±30); conversely, we administered colchicine for an average duration of 250.12 days (SD ±80.7). Relapses of IRS were reported in 1/3 of cases who had discontinued therapies.

CONCLUSIONS: The overall duration of treatments to manage IRS has a weight in terms of patients' outcome. A reduced duration of therapy with corticosteroids and a longer duration of therapy with NSAIDs determine a longer disease-free interval. A significant discriminating effect in terms of risk of IRS recurrence relies in an earlier combination therapy with colchicine independently from the start with either NSAIDs or corticosteroids. Finally, the evaluation of genes causing autoinflammatory diseases has not revealed any pathogenetic variants in a subcohort of 20/57 patients with IRS.

Key Words:
Idiopathic recurrent serositis, Autoinflammation, Colchicine.

Introduction

Serositis is the inflammation of serous membranes variably associated with effusion: we usually talk about "recurrent" serositis when two acute episodes occur after an interval of at least 4 weeks from each other. Among main causes of serositis there are infections, neoplasms and autoimmune disorders[1], although numerous cases occurring in the apparent absence of any triggering disease have been reported, which are named idiopathic recurrent serositis (IRS). For such cases, it was supposed an autoinflammatory origin, caused by dysregulated activation of innate immunity[2]. However, at present, a gene potentially responsible for IRS has not yet been identified, while genes notoriously involved in autoinflammation have been found mutated in a very small percentage of cases[3].

From the epidemiological point of view there are no definite data in the medical literature concerning either incidence or recurrence rates of IRS, while there are a lot of data related to small series of patients with idiopathic recurrent pericarditis. In this regard, it was estimated that acute pericarditis has an incidence of 27.7 cases per

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100,000 individuals, and would be responsible for 5% of emergency visits due to chest pain[4,5]. Acute pericarditis can show a recurrent pattern in 10-to-30% of cases[6,7], while recurrent pericarditis is idiopathic in about 70% of cases[8].

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent the therapy of choice for acute episodes of idiopathic pericarditis[9], and they are usually preferred to corticosteroids. A multi-centre analysis found that corticosteroids were associated with higher rates of relapses, mostly when administered at full doses[10]. In light of these data, corticosteroids are currently considered a second line option, reserved for patients presenting contraindications or resistance to NSAIDs. Additionally, the use of colchicine is widely recognized as a tool for preventing recurrences of serositis. Specifically, the probability of relapses of pericarditis has been reduced since the introduction of colchicine[11-15]. Another line of treatment is represented by triple therapy with NSAIDs, corticosteroids and colchicine: the efficacy of this scheme was proved by observational studies that showed the need for a slow tapering of one drug at a time, from the corticosteroid to colchicine[16]. Another further therapeutic option is represented by interleukin-1 (IL-1) blockers[17-19], in particular the recombinant human IL-1 receptor antagonist anakinra, largely used in the management of different autoinflammatory disorders[20-23]. However, if there is a broad consensus on which therapeutic options to use in the acute phase of pericarditis on one hand, there are few data to suggest the optimal overall duration of treatment. As regards IRS, unfortunately there are no data suggesting the best treatment modality of acute episodes and/or relapses.

Aim of this retrospective study was to evaluate outcome and recurrence rates of patients with IRS by comparing the therapeutic approach and management modalities between first level centres and the Periodic Fever and Rare Diseases Research Centre in the Gemelli Hospital (Rome, Italy). An additional aim was to evaluate the presence of pathogenic variants for genes causing autoinflammatory diseases in a subcohort of patients with IRS.

Patients and Methods

A retrospective study was conducted at the Periodic Fever and Rare Diseases Research Centre of the Gemelli Hospital (Rome, Italy) to assess patients with history of IRS evaluated during the period 1998-2017. Inclusion criteria were age over 18 years and at least two episodes of a documented serositis. Patients who presented serositis in the context of infectious, neoplastic, autoimmune, hematologic or metabolic disorders and those undergoing a recent surgery were excluded. In addition, patients lost at follow-up for more than 5 years were excluded, because available data would have not allowed a reliable analysis. The total number of enrolled patients turned out to be 57. We decided to divide the whole sample in two subgroups: a first comprising patients arrived at our observation at the first recurrence of serositis and, therefore, at the second episode of serositis, for a total of 27 patients; a second subgroup included patients who came at our observation after at least two episodes of serositis, for a total of 30 patients.

In both subgroups we recorded family history for eventual autoimmune or autoinflammatory disorders, age at onset, number of episodes of serositis, clinical signs (pericardial and/or pleural rubbing, increase in the inflammation indexes, ECG alterations, serosal effusions) or symptoms (chest pain, abdominal pain, back pain, fatigue, dyspnea, vomiting, nausea, arthralgia, cough). Furthermore, we collected data about therapies administered for each acute episode, as well as information about the possible occurrence of fever of unknown origin combined with serositis. We also found patients who, on the basis of a suggestive clinical picture or having a family history positive for recurrent fevers and/or recurrent serositis, underwent genotype analysis to search for potential mutations in the autoinflammation-related genes. In particular, 14 patients were tested for mutation detection in the *MEFV* and *TNFRSF1A* genes, respectively involved in familial Mediterranean fever (FMF) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS), *via* Sanger sequencing method, and 6 patients, due to their clinical complexity, *via* Next Generation Sequencing (NGS) technique, which explored variants in a panel of 10 genes involved in autoinflammation.

Statistical Analysis

Statistical analysis was conducted separately on both subgroups of patients with IRS. We expressed descriptive statistics as mean and standard deviation (SD) for quantitative variables, while counts and percentages of frequencies were used to describe the binary variables. Data were

entered in a database specifically created using a Microsoft Excel program, and analyzed using SPSS Statistics spreadsheet for correlation and linear regression analysis. Statistical significance was set for p-values <0.05.

Results

The whole sample included 57 patients with IRS, 32 females and 25 males. Their average age at onset was 41.8 ± 18.2 years, and average age at the time of data analysis was 51 ± 30 years. Serosal manifestations were thus distributed: 25 patients presented pericarditis (43.8%), 2 pleuritis (3.5%), 20 pleuro-pericarditis (35%), 1 peritonitis and pericarditis (1.7%), 1 peritonitis and pleuritis (1.7%) and 8 subjects (14%) had a concomitant involvement of three serosal membranes, who were classified as having polyserositis (Figure 1).

In the first subgroup (27 patients) it was performed a linear correlation and regression analysis aimed at identifying a relationship between duration of treatment and disease-free interval. For these patients, both therapies given at the hospital of origin and at our Research Centre were analyzed in combination with recurrence rates. For the second subgroup (30 patients) the fragmentary reconstruction of therapies administered prior to the observation period did not allow a strict statistical approach equal to the first one.

In the first subgroup we found that 8 out of 27 received NSAIDs; 7 were treated with corticosteroids; 3 received corticosteroids and NSAIDs; 2 were treated with NSAIDs and colchicine; 2 with corticosteroid and colchicine; 1 with acetylsalicylic acid and colchicine; only 1 patient received a triple therapy (corticosteroid, NSAID, colchicine) as early as the first episode. For 3 patients it was not possible to trace the therapy. The mean duration of treatment with NSAIDs was 43.8 days (SD ±27.4); the mean duration of treatment with corticosteroids was 101.5 days (SD ±56.4). The mean disease-free interval in the case of NSAID treatment was 54.3 days (SD ±73.7), and in the case of corticosteroids 6.5 days (SD ±5.3). Regardless of therapy, the mean disease-free interval was 30.3 days (SD ±52.2). The mean duration of corticosteroid treatment appeared higher compared with NSAIDs. Therefore, we carried out a linear regression analysis in order to find a statistically significant correlation between treatment duration and disease-free interval. Evaluating the therapy as a whole, regardless of the drug used, the regression analysis did not show any substantial correlation (R2=0.00138, p=0.86). However, increasing the duration of treatment also the disease-free interval tended slightly to increase. After differentiating results by type of treatment, it was shown that for patients treated with NSAIDs the duration of treatment was directly related to a longer disease-free period (R2=0.73677, p=0.006). Conversely, for patients who were treated only with corticosteroids, the increase in the duration of therapy corresponded to a reduction of the disease-free interval (R2=0.60465, p=0.03).

For those admitted, the therapeutic approach was different. One out of 27 was treated exclusively with NSAIDs; 1 was treated exclusively with the corticosteroid; 2 were treated at the same time with corticosteroid and NSAIDs; 14 took NSAIDs and colchicine; 8 corticosteroid and colchicine; 1

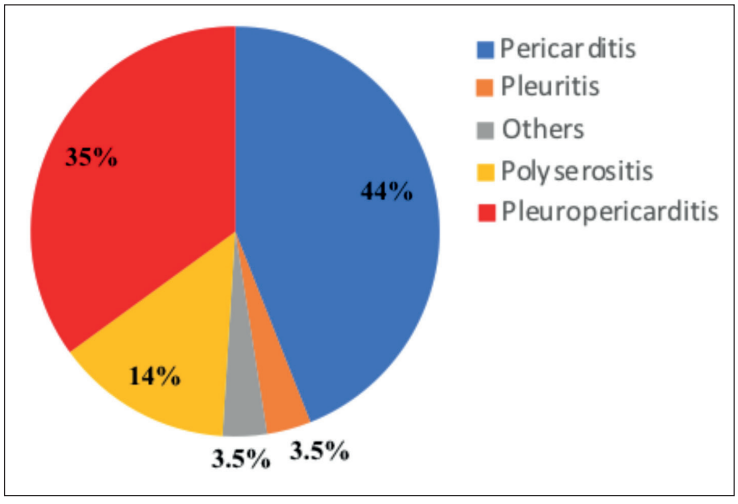

Figure 1. Distribution of cases of idiopathic recurrent serositis (IRS) in the whole study group.

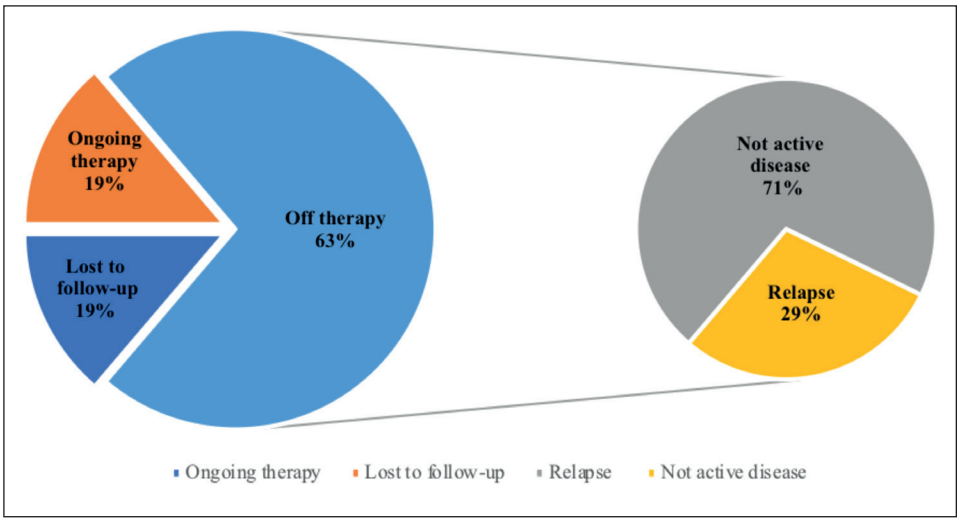

Figure 2. Percentage of recurrence rates of IRS in the first subgroup comprising patients admission at the Gemelli Centre at their first disease recurrence (and therefore at the second episode of serositis): 29% of those who had stopped therapy presented a relapse.

acetylsalicylic acid and colchicine, while no patient received a triple therapy. At the time of data analysis, 5 patients (19%) were still being treated: of these, 3 were still receiving NSAIDs in combination with colchicine, while 2 patients were only treated with colchicine. Five patients (18%) were considered lost at the follow-up. The remaining 17 patients (63%) had stopped treatment for at least 8 months. During this observation period we observed a relapse in 5 patients (29% of cases), at least 4 weeks after treatment stop, while 12 patients (71%) remained asymptomatic and their inflammatory parameters were within a normal range (Figure 2).

We also analyzed the main differences between treatments adopted in our Research Centre and in other first-level hospitals to better identify any eventual factors contributing to the recurrence. In terms of therapy, the most significant fact was that we largely used combined treatments compared to the predilection of monotherapy. Of note, 14 patients (52%) out of 27 were treated with NSAIDs and colchicine, compared with only 2 (7.4%) previously treated with this combination. Furthermore, corticosteroids were used in only 1 case at our Centre against 7 from other centres (Figure 3).

In terms of mean duration of treatment during acute phases, we found that it was 43.8 days (SD ±27.40) for NSAIDs in other hospitals, while it was 191.25 days (SD ±42.23) in our Centre (Figure 4). The mean duration of treatment with corticosteroids in other hospitals was 101.5 days (SD ±56.40) and 180.7 days (SD ±84.87) in our Centre, respectively.

The use of colchicine as a maintenance therapy represented a crucial difference. In other hospitals, when used, colchicine was administered

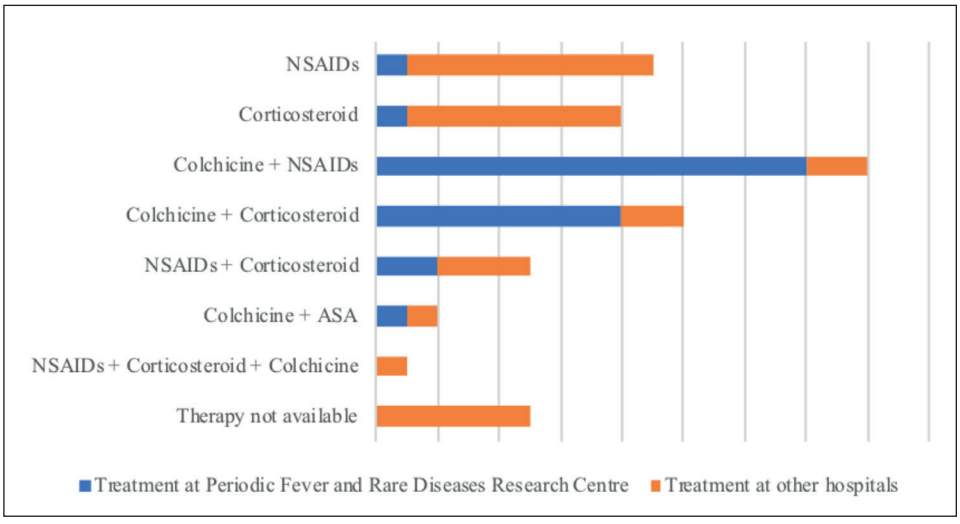

Figure 3. Comparison between therapies given to patients with IRS at the Gemelli Centre and in other centres.

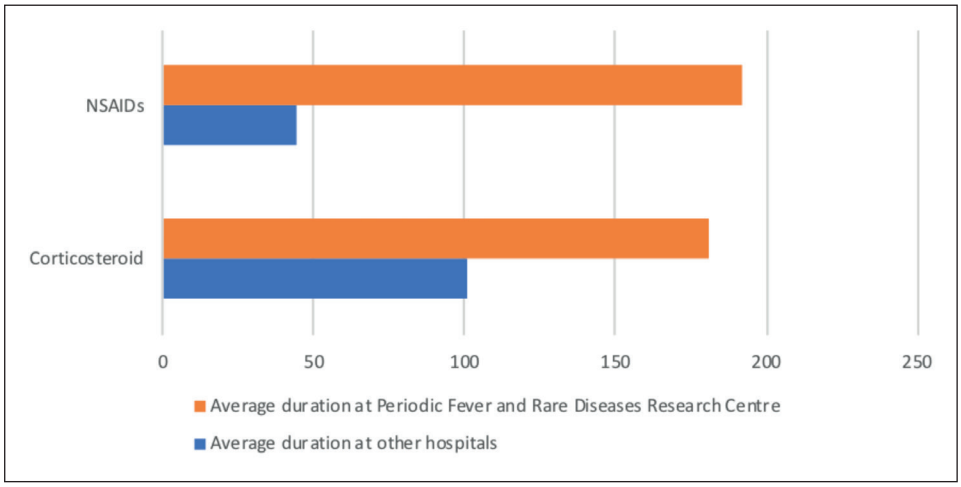

Figure 4. Comparison between the mean duration of therapies in patients with IRS evaluated at the Gemelli Centre and in other centres.

for a mean duration of 111 days (SD ±30), similar to NSAIDs or corticosteroids. Conversely, we administered colchicine for a mean time of 250.12 days (SD ±80.7), and its administration has continued even after NSAID suspension or in association with corticosteroids.

In the second subgroup of our study, including 30 patients with IRS who came to our observation after occurrence of at least two episodes, it was not possible to perform a rigid statistical approach, due to the fragmentary reconstruction of therapies administered prior to our observation. At the time of taking charge of these patients, the mean number of recurrences was 5 (SD ±2). For patients with an active disease (n=16) the following therapeutic approaches were used: 1 took only NSAID, 1 triple therapy, 1 anakinra, 1 acetylsalicylic acid and prednisone, 6 NSAID and colchicine, 3 prednisone and colchicine, 3 prednisone and NSAID. For patients who were not in an active phase of disease (n=14), 13 were treated with colchicine and 1 with hydroxychloroquine. At the time of data analysis, 7 patients (23.3%) were lost at follow-up, 5 patients (16.6%) were still on treatment, and the remaining 18 (60%) had stopped treatment for at least 8 months. During the period of observation, a relapse was observed in 33.3% of cases (6 patients); the remaining 12 (66.6%) remained asymptomatic with inflammatory parameters within the normal limits (Figure 5).

Among 6 patients who relapsed, 4 came to our observation with an active disease. In addition, we observed that 2 patients relapsed while on corticosteroid tapering; 1 patient relapsed in the colchicine-dose adjustment phase; the last patient, finally, showing to be resistant to all medical therapies, relapsed after discontinuation of IL-1 blockers. Conversely, among patients who

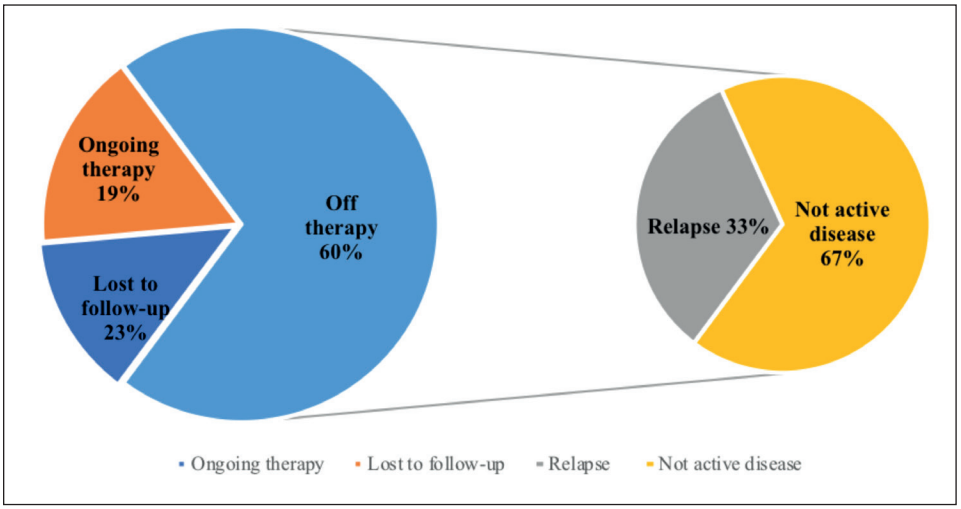

Figure 5. Percentage of recurrence of IRS in the second subgroup comprising patients arrived at the Gemelli Centre after occurrence of at least two episodes of IRS: 33% of those who had stopped therapy presented a relapse.

came to our observation in a free-disease phase, only 2 relapsed. It is important to emphasize that relapses occurred only after suspension of colchicine (because of general colchicine-related side effects, such as abdominal pain or diarrhea).

Analyzing retrospectively our study group with IRS, we found that 20 out of 57 patients underwent genetic analysis at the search for autoinflammation-related mutations, based on their clinical features or family history of recurrent fevers and/or recurrent serositis. For 14 patients, analysis for FMF and TRAPS mutations was performed using the Sanger method: we found that 6 patients were wild-type in the related genes, while 8 patients were negative for *TNFRSF1A* mutations and positive for some peculiar *MEFV* variants. In particular, the variants *E148Q*, *I591T* and *R329H* were found in heterozygosity in 3 single patients, the variant *R202Q* in heterozygosity in 2 patients, and the variants *G148G*/*P369S*/*A408G* in heterozygosity in 1 patient. For 6 patients, the search for mutations in a panel of 10 genes (*MEFV*, *TNFRSF1A*, *MVK, NLRP3, NLRP12, PSTPIP1, IL1RN, LP1N2, NOD2, PSMB8*) using the NGS technique revealed 3 patients wild-type and 3 patients carrying in heterozygosity the *E148Q* and *M680I* variants on the *MEFV* gene and the *T341I* variant on the *NLRP12* gene, respectively.

Discussion

IRS is a poorly studied disease, although frequently encountered in the everyday clinical practice, associated with a wide range of disorders but also without any known underlying condition[1]. The exact pathogenesis of IRS remains unknown. For a long time, IRS was considered an autoimmune condition, given its frequent association with different rheumatological diseases[2]. However, recent observations and different therapeutic experiences have linked this mysterious condition to hereditary autoinflammatory disorders, which are basically characterized by recurrent attacks of fever and serous inflammation, with a major complication represented by the insidious development of secondary amyloidosis[24-27]. In particular, mostly FMF[28] and TRAPS[29] can be heralded by the recurrence of serositis variably combined with other symptoms and fevers[30-32].

Supporting the hypothesis that IRS is likely to have an autoinflammatory pathogenesis, many elements should be considered: elevation of the inflammatory markers during acute episodes and their constant negativity during intercritical periods[33], efficacy of colchicine and IL-1 antagonists in the prevention of recurrences[11,20,23,28,29], and evidence of familiar clusters of patients with serositis[7,30]. Probably, IRS can be placed at a borderline between these two major categories of diseases, which are much less distant than we have always imagined. The management of IRS is undefined in the medical literature, and guidelines[34] exist only in regard to idiopathic recurrent pericarditis.

In this study we have compared different therapeutic approaches adopted in adults with IRS.

First of all, what has emerged is the strong heterogeneity in treatment strategies for the whole cohort. In particular, with regard to pericarditis, we have observed that the therapeutic approach used by various centres often diverged from what suggested by the general guidelines for the diagnosis and management of pericardial diseases, drafted from the European Society of Cardiology[34]. Furthermore, we observed that there is no clear consensus on the total duration of therapy. In fact, the cited guidelines suggest reducing therapy based on patients' symptoms and inflammatory markers, but do not indicate a precise timing for dose reduction[34].

To increase the reliability of our investigation, we divided the whole sample into two subgroups. From the analysis of the first one, including patients with IRS admitted to our Centre at the second episode, it emerged that the overall duration of a previous treatment with NSAIDs was directly related to the disease-free period (p=0.006). The linear regression analysis regarding the use of corticosteroids before our intervention confirmed that a longer therapy corresponded to a reduced free-disease interval (p=0.03). As recognized by the medical literature, corticosteroids administered without adequate tapering or at higher doses could cause immediate resolution of symptoms, but also enhance the risk of recurrence and steroid-dependence[10]. Hence, corticosteroids should be used at the lowest doses and for the shortest period possible. This suggestion seems to disagree with our findings, since our patients treated with corticosteroids for longer periods and slowly decreasing the amount of steroid presented a lower recurrence rate in the mid-long term. Our therapeutic choice was established for patients who had already presented a relapse and who, in most cases, had become steroid-dependent. In addition, we observed that the overall duration of treatment contributes to prognosis and that the use of col-

chicine has a significant discriminating effect in terms of recurrence risk, regardless of its association with NSAIDs or corticosteroids as early as the first episode.

Analyzing the second subgroup, the lack of complete data did not allow a rigorous analysis, as regards therapies used before patients' admission at our Periodic Fever Centre. Step-by-step tapering of all drugs has reduced the overall relapse rate, regardless of patients' previous medical history.

For both subgroups, attack therapy with NSAIDs, corticosteroids and/or IL-1 blockers has proven to be effective in resolving acute symptoms of IRS.

Analyzing the overall data, we highlighted that the recurrence rate was similar in the two subgroups (29% *vs.* 33%). For the prevention of relapses, none of the three drugs could be considered effective alone, but the administration of colchicine determined a significant reduction in the recurrence rate.

Genotype analysis of genes classically associated with autoinflammatory diseases revealed peculiar variants in 11 patients out of the 20 screened. Among the mutations detected, only one *MEFV* variant could be considered relevant for the expression of FMF, if in homozygosity. In our case, this mutation occurred in heterozygosity and, therefore, could not clearly explain the phenotype of that patient. All other mutations found, instead, could be classified as polymorphisms or variants of unknown significance.

Conclusions

In summary, the statistical analysis applied to our cohort of 57 unselected patients with history of IRS managed during the period 1998-2017 has revealed that the overall duration of treatment has a role in determining patients' outcome. Namely, a longer treatment with corticosteroids slowly tapered over time determines a longer disease-free interval and also a lower risk of steroid dependence. A longer disease-free interval is concurrently related to the overall duration of therapy with NSAIDs. This retrospective analysis has revealed that earlier introduction of colchicine is associated with a lower risk of IRS recurrence, being not influenced by NSAIDs or corticosteroids. Furthermore, genotype analysis of genes causing autoinflammatory diseases in a subcohort of 20 patients with IRS has not disclosed any clearly pathogenetic variants.

Conflict of Interests

The authors declare that they have no conflict of interests.

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