Clinical Communications

Persistence of disease flares is associated with an inadequate colchicine dose in familial Mediterranean fever: a national multi center longitudinal study

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Clinical Implications

- In real life, almost 30% of patients with familial Mediterranean fever display a persistent disease activity not fulfilling the definition of colchicine resistance, but impacting their quality of life. In most of them, colchicine is underdosed and maximum recommended dose is rarely used.

Familial Mediterranean fever (FMF) is characterized by self-limited episodes of fever and polyserositis.[1] *MEFV* gene encodes for a protein named Pyrin, which plays a pivotal role in the activation and secretion of IL-1.[2] Daily colchicine is highly effective in preventing attacks in this disorder in a dose-related fashion.[3] Many definitions of colchicine resistance are available in the literature. The European League Against Rheumatism (EULAR) guidelines defined resistance as one or more attacks per month in compliant patients who had been receiving the maximally tolerated dose for at least 6 months.[4] A similar definition was confirmed by a recent consensus among experts.[5] In the present national multicentric longitudinal study, we analyze the impact of colchicine treatment on disease activity and quality of life in real life in pediatric and adult patients with FMF.

Twenty centers enrolled their patients in the longitudinal version of the Eurofever registry.[6] Response to treatment was defined as *complete* (absence of clinical manifestations and normal laboratory parameters), or *incomplete* (persistence of fever episodes and/or some elevation of acute phase reactants). *Incomplete responders* were further classified as: (1) *resistant* (≥1 episode/month),[4,5] (2) *partial responders* (<1 episode/month), and (3) *partial responders with unknown frequency* (ie, patients presenting episodes without information on their frequency). Starting and maximum doses of colchicine were considered according to EULAR recommendations.[4,5] A specific questionnaire on compliance (adapted from Ben-Chetrit and Aamar[7]) and some aspects of the quality of life (limitations in daily activity, chronic fatigue or pain, and loss of school/workdays) were also collected (see this article's Online Repository at www.jaci-inpractice.org), as recently indicated as basic information for the evaluation of the response to colchicine in FMF.[5] In January 2020, complete baseline information was available for 341 Italian patients with FMF in the registry: 262 patients had at least 1 longitudinal follow-up visit and were eligible for the study; 221 (125 children, 91.2%; 96 adults, 96.9%) were treated exclusively with colchicine, with a median follow-up of 3.7 years (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). At the last follow-up visit, 122 (55.2%) displayed a *complete response*, 17 (7.7%) were classified as *resistant* (≥1 episode/month), 65 (29.4%) as *incomplete responders* (<1 episode/month), and 17 (7.7%) as *incomplete responders with unknown frequency*. The pattern of response to colchicine according to the different age groups is reported in Figure 1. Among patients (65) with an *incomplete response* (<1 episode/month), 37 (59%) displayed 1 to 3 episodes/year (26.2%, 1 episode/year; 20%, 2 episodes; 15.4%, 3 episodes), 15 (21%) displayed 4 to 5 episodes/year (10.7%, 4 episodes; 7.7%, 5 episodes), and 13 (20%) displayed ≥6 episodes/year (13.9%, 6 episodes; 1.5%, 7 episodes; 4.6%, 8 episodes). Overall, patients with *incomplete response* displayed a mean reduction of 10 fever episodes/year (range, 0-18) in respect to the precolchicine observation.

In Table I, median colchicine dose in different age groups, expressed as daily dosage and mg/kg/day, is reported in accordance with response to treatment. Overall, 54 patients with residual disease activity (24.4% of the whole population) were still on their colchicine starting dose, especially in the pediatric subgroup (19 of 48 children with residual disease activity, 39.5%). Among these patients, the presence of side effects possibly related to colchicine was reported in 4 patients only (diarrhea 2 patients, vomiting 1 patient, myalgia 1 patient). None of the patients treated with colchicine reached the maximal recommended colchicine dose (1-3 mg/day according to the age group)[5,6] (Table I). Data on compliance and quality of life were available for 174 patients. One hundred forty-five (83.3%) declared an optimal compliance (compliant to >90% of prescriptions), 20 (11.5%) a good compliance (between 50% and 90% of prescriptions), 3 (1.7%) a poor compliance (<50% of prescriptions), and 6 (3.5%) patients were noncompliant at all. An optimal compliance was observed in 88% of patients with complete response, 76% of incomplete responders, and 73% of resistant patients. Overall, 58 (33.3%) patients reported a limitation in at least 1 item related to the quality of life (limitation of daily activity, presence of chronic pain or fatigue, loss of days of