Editorial

Non-response to colchicine in FMF – definition, causes and suggested solutions

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Problem presentation

About 5-15% of patients with familial Mediterranian fever (FMF) do not respond to treatment with colchicine (1, 2). This relatively wide range is derived from the general impression of physicians dealing with the disease rather than from a careful and thorough epidemiological study.

Such numbers raise questions regarding the definition of 'non-responders' that could explain the wide range since every physician uses his own criteria when dealing with FMF patients.

Why we need to define the criteria for colchicine non-responders

In order to evaluate the real efficacy of colchicine in FMF and the exact proportion of those who do not respond to the drug, we must have clear criteria defining a 'non-response'. Such a definition would furthermore help us to understand the causes leading to a non-response when investigating the mechanism of action of colchicine. The definition of "non-response" will aid physicians in choosing those FMF patients who are eligible for other treatments following the failure of colchicine. Such a decision is not trivial, considering the long-term adverse effects and risks of the alternative medications (3-6).

Since there is no *in vivo* functional assay to measure the effect of colchicine – as is the case with aspirin – physicians must rely on the patients' statements regarding their clinical response to this medication (7). Therefore, one must be careful to distinguish between "false" non-responders who did not receive an optimal treatment and "true" non-responders who did. In "false" non-responders, management of the factors leading to a non-response or the improvement of tolerance to colchicine may allow the optimization of re-treatment and a chance of disease suppression. On the other hand, in "true" non-responders the probability of achieving control of the disease with re-treatment is very low and one must seek a new approach or new medications to prevent FMF attacks.

Problems raised by the current definition

In recent reports, authors have defined "non-responders" as patients who experienced FMF attacks at a frequency greater than once every 3 months despite treatment with 2 mg colchicine daily (1, 8). In the anti-Il-1beta treatment protocol for FMF, subjects were adjudged to be non-responsive to colchicine (up to 2 mg per day) on the basis of continued symptoms or flares (≥one per month) or elevated acute phase reactants (ESR, CRP or SAA ≥1.5 times the upper limit of normal between attacks) despite treatment with maximally tolerated doses of colchicine (NIAMS: Clinicaltrials.gov., NCT00094900, Interleukin-1 trap in the treatment of autoinflammatory diseases).

These definitions may not be applicable in some cases and cannot be applied everywhere by everyone. For example, we do not give a 7-year-old FMF patient 2.0 mg colchicine daily. According to the above criterion we cannot define a child as a non-responder unless he takes 2 mg colchicine daily. And what about an overweight patient (90-100 kg)? Are we sure that 2 mg colchicine is enough to control FMF attacks in such a case? Furthermore, if a patient has an attack every week or two, and following colchicine treatment he has a single attack every 3 months will we consider it as a response or should we add a new category – a "partial response" – rather than consider

the treatment a total failure? Should we designate a complete response only if the patient does not experience any attack following the administration of colchicine?

If we adopt this approach what percentage should be considered as a partial response – a 10% reduction in attacks or a 90% reduction in attacks? Furthermore, what about the effect of the treatment on the severity of the attack? Will a reduction in disease severity be considered a response?

We know there are several triggers that may induce or aggravate FMF attacks. Extreme physical exercise, emotional stress, concurrent infection, exposure to cold, and menstruation are some of these (9). If a patient treated with colchicine regularly and continuously experiences an FMF attack following one of these triggers, do we consider this a failure of the drug or not?

Another major question is: when a patient on colchicine treatment does not have FMF attacks but still has elevated acute phase reactants, should he be defined as a non-responder?

Thus, it seems that we have to try to refine the definition of non-responders to colchicine treatment so that some of the questions raised above are answered.

What is the maximal dose before claiming treatment failure?

An important point to be discussed is at which dose of colchicine do we claim treatment failure? At a fixed dose (for example, 2.0 mg) or at the maximal dose tolerated by the FMF patient? Would it be considered as a failure only after the administration of intravenous colchicine in addition to the regular oral dose?

Regarding this issue we must take into account the properties of the different colchicine preparations, their bioavailability, concurrent medications being taken by the patient, and physiological factors that may differ among FMF patients.

In order to claim that the medication has failed, one should demonstrate that it reached therapeutic levels in a given patient. Here we face another problem of definition – how to measure the drug level. Does the plasma level correlate with the clinical response? In a study by Livneh *et al*. it was shown that the clinical features of FMF did not correlate with plasma levels, but did correlate with colchicine levels in monocytes (8). On the other hand, the colchicine dose did correlate with plasma and neutrophils levels (10). So where should we measure colchicine levels – in the plasma, in the polymorphonuclear cells, mononuclear cells or in the lymphocytes? Should we check the drug level in the tissues (*e.g*., serous membrane) involved during the FMF attack?

Another problem concerns the appropriate method for measuring colchicine. The radioimmunoassay has been used in recent studies, but its reproducibility and standardization between laboratories may pose a serious problem. Development of a more sensitive and accurate method based on mass spectrophotometry and HPLC techniques should be encouraged.

Suggested principles for the definition of non-responders

One way to solve many of these problems is to adopt the method of ACR20, 50 and 70, which is used to assess the effectiveness of rheumatoid arthritis treatments (11). In the case of FMF we need to decide, for example, that the basis of reference will be the annual rate of attacks in the propositus. If colchicine treatment reduces the rate by 20% we may call it an FMF-20 response; if colchicine decreases the number of attacks from 12 times to 6 times per year we will designate it FMF-50 response; and so on. This method has several advantages. First of all, it estimates the effect of colchicine in a given individual and compares the effect of colchicine in the same person before and after colchicine administration. Secondly, this method produces accurate values rather than a general estimation. Thirdly, it can be used in the future for the assessment of other medications that may be developed for FMF. Finally, this method does not depend on ethnicity, gender, type of preparation, etc. and it can be applied to both adults and children.

Nevertheless, in order to define an FMF patient as a non-responder we have to be sure that he is fully compliant. This can be validated by measuring the plasma level of colchicine, since plasma levels have shown a good correlation with the dose ingested. Regarding the choice of method for measuring colchicine, we must determine which is the method most widely used in most countries and attempt to standardize the units internationally.

A reduction in the severity and duration of the attacks without a reduction in the number of attacks is not counted as a response in the current definition. One can take note of the fact, but it is not to be considered a response. Alternatively, it is possible to use the currently available severity score and report it in parallel with the response score.

Regarding the issue of acute phase reactants (AFR), it appears that AFR should not be included in the definition of "response". We must limit our definition solely to the clinical response. Furthermore, it is expected that those who respond clinically will experience a parallel decrease in the acute phase reactants. Since these are not specific for FMF, one should exclude other forms of occult inflammation in the asymptomatic patient in whom AFR levels are elevated.

Finally, we have to define the maximal colchicine dosage based on the weight of the patient. Two mg daily for patients whose weight is between 40 to 80 kg is reasonable. For those who are over 80 kg and up to 100 kg, we propose to define 2.5 mg daily as the maximal dose before claiming treatment failure. Since it has been shown that patients who do not respond to 2 mg usually do not improve with a further increase in the dose, we suggest not including the need for an intravenous dose of colchicine in addition to the maximal dose (8). Recently the FDA prohibited the use of intravenous colchicine in the USA, thus further justifying our present suggestion.

Possible causes for a non-response

Since colchicine has to go through several stages on its way to controlling inflammation, there are various points at which its efficacy may be affected. Theoretically, problems with its absorption in the intestine can change

the therapeutic plasma levels. Problems with the functioning of the MDR1 gene (P-glycoprotein pump) in white blood cells or serous membrane cells can also affect colchicine function (12, 13). Modulation of colchicine metabolism by different factors (erythromycin, clarithromycyn, lovastatin, simvastatin, cyclosporin, grapefruit juice, St. John's wort, etc.) at the level of cytochrome 3A4 can also influence the effect of colchicine (14). The search for the cause(s) of colchicine ineffectiveness may bring to light ways of circumventing them, thus allowing a new trial of colchicine before making a final decision regarding its failure.

Treatment options for non-responders

Recently, anecdotal data has been reported on the use of thalidomide, anti-TNF agents and anti-IL-1 agents (such as anakinra) in FMF patients who have been classified as non-responders (3-6). In most patients these agents controlled the FMF attacks quite effectively. However, these medications are not without side effects and one must ensure that the colchicine treatment was administered adequately and to the maximum before claiming its failure. Furthermore, we know that one of the most important advantages of colchicine is its potential to prevent and even reverse amyloidosis. An important question remains as to whether biological agents can prevent amyloidosis as well.

The use of expensive biological medications is of major significance since the populations in which FMF is widespread are generally poor and patients may not be able to afford the life-long treatment that is necessary. For example, in Israel the cost per year for colchicine is $60, whereas the cost for Remicade is about $32,000 per year. Therefore, the accurate identification of those FMF patients who are not responsive to colchicine and who may require these medications is of the utmost importance.

We propose this new method in order to draw the attention of our readers and colleagues to this problem. We hope that our proposal will launch a fresh and critical debate to help resolve the issue of the definition of colchicine non-responders.

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