Editorial

About colchicine compliance, resistance and virulence…

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent attacks of fever and peritonitis, pleuritis, arthritis or erysipelas-like erythema (1). Since 1972, colchicine has been the drug of choice for preventing FMF attacks as well as its devastating complication-amyloidosis (2, 3). Nevertheless, some patients with FMF do not respond to this treatment. The rate of non-responders ranges from 5 to 15% of the patients (4, 5).

Last year we addressed the issue of non response to colchicine, raising the problem of defining this term and suggesting ways to solve it (6). One of the major problems raised was that of *non-compliant* FMF patients who are considered to be non-responders.

Recently we tried to examine the rate of compliance in a small cohort of FMF patients in the clinic of one of us (SA). We followed 38 FMF patients whose ages ranged from 7 to 57 (21.92+13.61) (mean+SD). Fourteen of them were under the age of 12 years old. We checked how many prescriptions for colchicine they received from their physician during the last year and how many of them were actually filled. Since both actions (prescribing prescriptions and filling them) were fully computerized we could easily retrieve these data. Surprisingly, we found that only 5 patients (13%) filled all the colchicine prescriptions they received from their physician. Three of them (8%) did not fill any of them while 13 FMF patients (34%) filled less than 50% of the prescriptions they got that year. These findings show that more than 40% of the patients actually had poor compliance, raising a serious question regarding our estimations and definitions of "colchicine non-responders". Since most probably many of them are in fact non-compliant, it seems that previous reports overestimated the real rates of non responders. Furthermore, the present observation calls for more investment in our educational efforts for FMF patients in order to improve their compliance and response.

In previous studies it was shown that colchicine levels in neutrophils is higher than that of lymphomonocytes (7, 8). Since neutrophils play a major role in inflammation, the relative higher concentration of colchicine in these cells could explain its beneficial effect in FMF. Colchicine binds intracellular tubulin thereby inhibiting neutrophils chemotaxis suppressing the inflammatory process. However, the reason for the high concentration of colchicine in neutrophils compared with lymphomonocytes was not clear. P-glycoprotein is an integral membrane protein that serves as an energy-dependent transport peptide of diverse medications and substrates. The quantity of this protein in neutrophils is lower than that of lymphomonocytes. Therefore, we hypothesized that since in PMNs the p-glycoprotein pump has a low functional capacity due to its low quantity, the colchicine which enters the cells is not effluxed (8). In contrast, in lymphocytes the basic levels of colchicine are lower because it is effluxed immediately from the cells by the high activity of the p-glycoprotein pump. In a study by Lidar *et al*. where the authors tried to characterize FMF patients who are non-responders to colchicine, they found that colchicine levels in lymphomonocytes of these patients was 2-fold lower compared with that of lymphomonocytes in the responders group (9). The authors concluded that inadequate concentration of colchicine in lymphomonocytes may be responsible for their non-response. In order to further confirm this hypothesis they looked for different polymorphisms in the ABCB1 gene [the gene encoding the p-glycoprotein, formerly called

multiple resistant drug (MDR-1) gene] among responder and non-responder FMF patients (10). In a study by Bezalel *et al*. in this issue of the supplement, the authors failed to show any difference between responders and non-responders regarding their ABCB1 polymorphisms (C3435T). Responders and non-responders had higher and lower colchicine levels in lymphocytes irrespective of their ABCB1 C3435T status. Paradoxically, *Tufan et al*. (11) reported that the ABCB1 3435TT genotype is related to colchicine responsiveness, findings which are not in accord with those of *Bezalel et al*. (10).

Since the main cell involved in FMF attacks is the neutrophil, it seems unlikely that concentrations of colchicine in lymphocytes play a role in this inflammatory process. The contradictory results between the above studies further support this notion.

Since colchicine has to go through several stages on its way to controlling inflammation, there are various points where its efficacy can be affected. Theoretically, problems in its absorption in the intestine can change the therapeutic plasma or tissue levels. Problems in the functions of the ABCB1 gene (P-glycoprotein pump) in white blood cells or serous membrane cells can also affect colchicine function. Enhancement of colchicine metabolism by different causes (concurrent drugs, food, etc.) at the level of CYP 3A4 can also influence the effect of colchicine (12). Thus, trying to look for the cause(s) of colchicine ineffectiveness in a single cell – lymphomonocyte – may not be the right way to solve the question of the non-responders. It is possible that in real non-responders to colchicine there needs to be several concomitant defects or disturbances (double or triple hits) in various cells or tissues. This complexity of requirements may explain the relative rarity of the phenomenon of colchicine non-response.

In non-responders, our medical armamentarium is quite limited. Some case reports suggested using anti-TNF agents or anti-IL-1 formulas in order to suppress FMF attacks. The problem with these therapeutic measures is their high cost on the one hand, and the long-term side effects (infections and malignancies) on the other. Furthermore, in contrast to colchicine, we do not yet have solid data regarding their effect in preventing the development of amyloidosis.

Also in this issue of the supplement, Rosenbaum *et al*. suggest additional weekly IV injection of colchicine for FMF patients who are non-responders to oral colchicine treatment (13). They report their experience in 5 patients. This is an open-labeled observational study and as such has its innate limitations. A similar study with 13 FMF patients resistant to colchicine was reported in 2003 by another group (14). The same results were obtained in both studies. The basic idea of additional IV colchicine may be of value but deserves some clarification. First, one should repeat the study in a randomized double-blinded fashion in order to exclude a placebo effect of IV injection. Second, the rationale behind the addition of IV colchicine is to try to increase plasma or tissue levels of the drug by direct intravenous injection. This may overcome the problem in patients in whom colchicine absorption is disturbed or in cases of low bioavailability of the oral formula. Regarding this possibility, it should be stressed that it is still unproven that the mechanisms of non-response depend on colchicine levels either in neutrophils (the active cell in inflammation) or in other tissue components. Thus, it may well be that the mechanism of non-response is more complex and may involve basic intracellular processes at the molecular level.

Intravenous colchicine injection bears a serious risk for the patient since its therapeutic range is very narrow as is the case with digoxin. As mentioned by Rosenbaum *et al*., in the United States IV colchicine is prohibited due to 2 fatal cases of treating patients with back pain. Although Rosenbaum *et al*. suggest reserving this mode of treatment only for young and healthy FMF patients with normal liver and kidney functions, it may still be dangerous. Patients may concomitantly take medications that may increase blood or tissues colchicine levels. For example, cyclosporine induced a 50% decrease in renal colchicine tubular clearance (15). Cimetidine, which inhibits CYP 3A4, is associated with a 32% decrease in colchicine hepatic clearance (16).

The main problem is the lack of measures to get rid of colchicine in case of intoxication. Dialysis does not remove colchicine and even high flux dialysis is ineffective for this purpose (17). In contrast to digoxin, anti-colchicine antibodies (Fabs) are not available although it was reported to be effective in colchicine intoxication (18).

In our opinion, one of the solutions to this problem would be an available easy and accurate method to measure colchicine. If we had such a method we could follow colchicine levels (in plasma or WBC) and feel more comfortable in raising the dose of the drug in those who do not respond and have low levels. Such a measurement would help us avoid colchicine intoxication.

In our daily practice we administer digoxin quite safely due to the availability of methods to measure the serum level of the drug. Can anyone imagine that we would give digoxin if we did not have a way to measure its blood levels?

We believe that the same approach should be adopted in the case of colchicine. Unless we develop method(s) to measure colchicine routinely, treatment with IV colchicine should be postponed.

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