TRENDS IN COLCHICINE TREATMENT IN FAMILIAL MEDITERRANEAN FEVER (FMF)

Micaela La Regina
Periodic Fevers Research Centre
Catholic University, Rome, Italy

micaela.laregina@rm.unicatt.it

Avi Livneh§, Raffaele Manna*, Huri Ozdogan# &
International Study Group for the evaluation of colchicine treatment in familial Mediterranean fever.

§Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, Israel
#Department of Rheumatology, Cerrahpasa Medical School, University of Istanbul, Turkey
Aims of the Study

- To collect data about current use in familial Mediterranean fever treatment worldwide
- To examine current needs and areas of uncertainty in colchicine use
- To obtain preliminary opinions about unresolved issues, such as colchicine response, intolerance, resistance
- As a first step towards reaching a consensus
Design of the Study

- 38 items agreed by the four main investigators (La Regina M, Livneh A, Manna R and Ozdogan H)
- Covering 7 areas of practical application:
Design of the Study

- Sent to approximately 50 physicians worldwide (source: participants of 4th International Congress, Bethesda 2005 and ISSAID members list) by e-mail
- Deadline 27th January 2008
- Clarification
- Collection of data
- Analysis of results
- Definition of “Trends” (list of answers common to more than 70% of physicians interviewed)
Results

- 24 completed questionnaires from 8 different countries
  - Turkey: 7
  - Armenia: 2
  - Israel: 5
  - The Netherlands: 2
  - Greece: 3
  - Spain: 1
  - Italy: 3
  - USA: 1

- Experience from a total of 4563 patients:
  - 1230 < 10 y.o.
  - 2473 > 20 y.o.

  91% from classically affected countries
  9% from non-classically affected countries

- Percentage of completion: >89.5%
- Questionnaires excluded: none
Physicians’ Experience

24 physicians:

average experience in colchicine use: 15.5 years
(range 5-30 years)

following a total of 458 patients per month (range 1-100 patients/month)

have published a total of 272 papers on FMF in international medical journals (updated to March 2008)
Dosages, Administration and Schedules
Dosages, Administration and Schedules. 2

<table>
<thead>
<tr>
<th>Sample</th>
<th>Initial Dose</th>
<th>Optimal Dose</th>
<th>Maximum Effective Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child &lt;5 years old</td>
<td>0.71</td>
<td>0.57</td>
<td>0.47</td>
</tr>
<tr>
<td>Child &gt;5 years old</td>
<td>0.62</td>
<td>0.60</td>
<td>0.76</td>
</tr>
<tr>
<td>Adult</td>
<td>0.65</td>
<td>0.66</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Relative Dispersion Index (d)  
0 ≤ d ≤ 1
Dosages, Administration and Schedules.

All the physicians involved prescribe colchicine *per os*. None prescribe i.v. colchicine during attacks.

74% of physicians prescribe fractioned doses (81% in adults, 69% in children). 20% prescribe a single dose, if tolerated.

73% increase the dosage stepwise with increments of 0.25-0.5 mg/d until a *clinical response* or *adverse effects* are observed.

All the physicians prescribe pain relievers during attacks:
- 58% NSAIDs
- 30% NSAIDs + pure analgesics
- 12.5% NSAIDs + steroids
Dosages, Administration and Schedules. 4

83% perform a diagnostic test with colchicine (43% regularly)

75% of physicians do not increase dosage before menses

83% do not increase dosage during attacks

85% continue with the same dosage during pregnancy

83% increase dosage in proteinuric/microalbuminuric patients, if tolerated
Side effects, Allergy, Drug Interactions. 1

In what proportion of your patients did you have to lower/stop colchicine?
Side effects, Allergy, Drug Interactions. 2

54% of the physicians prescribe a lactose-free diet to reduce gastrointestinal side-effects
18% probiotics
14% gastroprotective agents
14% loperamide

Only 2 physicians reported cases of allergy to colchicine (4 cases in total) and proposed 2 different desensitization protocols

Only 35% of physicians reported drug interactions:
13% with macrolides
13% with statins
4.5% with cyclosporin
4.5% with omeprazole
Efficacy and Toxicity Monitoring. 1

How do you monitor Colchicine dose?

A disappearance of attacks
B acute phase reactants
C severity assessment
D other ways
Efficacy and Toxicity Monitoring.

48% use a combination of the first 5 or 6 tests

Laboratory test frequency with responsive patients: 74% from every 6 to every 12 months
Efficacy and Toxicity Monitoring. 3

Do you consider a patient not responsive to Colchicine on the basis of
A Time duration of observation
B Number of attacks per year
C Abnormal APR during attack-free periods
D Colchicine dose equivalent to...
E Persistence of chronic manifestations
Efficacy and Toxicity Monitoring

Intolerant if the patient complains of...

Which disease manifestations do you think are not controlled by colchicine?
Criteria for Colchicine Intolerance Definition

Would you make a list of criteria for colchicine intolerance?
Would you make a list of criteria for colchicine resistance, in a compliant patient?
37.5% of physicians reported sporadic alternative treatments:

- 40% anti-TNFα/IFNα
- 30% Thalidomide
- 20% Azathioprine
- 10% Anti-IL1, Fluoxetine
Classically vs non-classically affected countries

**Dosages:** always higher in classically affected countries (CACs)

**Stepwise increase:** more frequent in non-CACs (80% vs 64%)

**Diagnostic Test:** more commonly used in CACs (92% vs 70%)

**Co increase during attacks:** less commonly in CACs (7% vs 30%)

**Co increase before menses:** more commonly in CACs (36% vs 20%)

**Pregnancy:** colchicine suspended slightly more often in non-CACs (28% vs 8%)

No differences in

**Dosage increase in proteinuric/microalbuminuric patients**

**Frequency of check-up in responsive patients**

**Laboratory tests to monitor efficacy and toxicity**
Current Trends in Colchicine Treatment in FMF

Colchicine is only administered *per os*

Fractioned doses and stepwise increases are largely preferred

Dosages: no real agreement observed; we feel it is essential to correlate dosages with body weight and/or body surface

A diagnostic test with colchicine is often done, although not on a regular basis

NSAIDS alone or in combination with pure analgesics are prescribed as additional drugs during attacks

Colchicine dosage is not increased before menses and during attacks but is increased in microalbuminuric/proteinuric patients, if tolerated

During pregnancy, it is not stopped and the same dosage is maintained
Colchicine dosage is evaluated on more than 1 criterion: attack disappearance and reduction of APR are the most commonly used.

Efficacy and toxicity are evaluated more frequently than once every 4 months in responsive patients. Urinalysis is the universal test of choice, followed by ESR, CRP, WBC and transaminases.

Unresponsive patients are defined by more than 2 criteria. A variable time of observation and the post-colchicine number of attacks are largely applied as criteria.

The main criterion for definition of colchicine intolerance is diarrhoea.
Two or more criteria are suggested to define colchicine resistant and intolerant patients

With regard to resistance, the main criteria recommended are changes in attack patterns (such as different degrees of change and characteristics of attacks) and persistence of abnormal APR

When defining intolerance, gastrointestinal symptoms are indicated as the main criterion
Next Steps

To re-analyze the results including the data from the questionnaires received after the deadline

To search current medical literature for answers to questions arising from this survey, before proceeding with the next survey

To develop a new questionnaire using a format created by the RAND Corporation to ascertain expert consensus (www.rand.org)

To create practical guidelines based on expert consensus
Acknowledgements

Livneh A., Israel
Manna R., Italy
Ozdogan H., Turkey

and the International Study Group for the evaluation of colchicine treatment in familial Mediterranean fever

Akar S.
Ayyazjan A., Armenia
Ben-chetrit E., Israel
Berkun Y., Israel
Direskeneli H., Turkey
Ekim M., Turkey
Elazary A.S., Israel
Fabio G., Italy
Frenkel J., The Netherlands
Gasparyan A., Armenia
Gattorno M., Italy
Goulielmos G., Greece
Konstantopoulos K., Greece
Korkmaz C., Turkey
O’Neil K., USA
Padeh S., Israel
Peleg H., Israel
Toribio Galeote R., Spain
Tunca M., Turkey
Verrecchia E., Italy
Vougiouka O., Greece
Wulfraat N.M., The Netherlands
If you are interested in joining the “Trendy Group”, please contact:
micaela.laregina@rm.unicatt.it