ROLE OF METHOTREXATE INTOLERANCE SEVERITY SCORE (MISS) IN RHEUMATOID ARTHRITIS TO KNOW METHOTREXATE INTOLERANCE: A 2-YEAR PROSPECTIVE STUDY.

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Abstract

Rheumatoid Arthritis is the most common inflammatory arthritis among all other inflammatory arthritis. Methotrexate is the mainstay drug in treatment of RA.

Objective: To determine the prevalence of methotrexate intolerance and importance of MISS as a tool to know methotrexate intolerance.

Materials and Methods: 150 pts of RA including 120 females and 30 males attending rheumatoid services of Sri Guru Ram Dass hospital from December 2013 to December 2015 were prescribed methotrexate as per protocol approved and were followed for methotrexate intolerance using MISS (Methotrexate intolerance severity score).

Results: Out of 150 pts of RA on methotrexate, 21 (14%) were found to have MISS >6.

Conclusion: MISS is a very important tool for application in rheumatoid arthritis to know MTX intolerance and timely intervention to reduce the MTX intolerance to prevent the incompliance for an otherwise very effective DMARDS in treatment of rheumatoid arthritis.

Introduction:

RA is the most common inflammatory arthritis that affects primarily the joint lining resulting in painful, swollen and warm joints. Wrist and hand are the most commonly involved joints with the same joints typically involved over both sides of body. About 24.5 million people are affected by rheumatoid arthritis, this is between 0.5-1% of the global population (1,2,3). If not treated in time and adequately, RA can lead to various deformities particularly of hands. After the introduction of DMARDS including MTX the deformities like Zdeformity, boutonniere deformity, Swan neck deformity have been reduced to a large extent. Methotrexate is the mainstay of almost all combination treatment regimens of RA and has resulted in enhanced efficacy over MTX alone, without added increase in side effects (4,5,6,7). To improve its compliance MTX intolerance parameters are looked for and required reducing actions taken to improve its compliance.

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Aim of our study was to detect the prevalence of gastrointestinal and behavioral symptoms before (anticipatory and associative) and after methotrexate ingestion and to calculate the usefulness of MISS score.

**Methods and material:**
150 patients of rheumatoid arthritis including 120 females and 30 males attending the rheumatology clinic of the hospital from June 2013 to December 2015 were prescribed methotrexate and followed for intolerance for methotrexate as per validated methotrexate intolerance severity score. MTX intolerance features were enquired at each visit which was of 4-6 weekly. Base line stomach ache, nausea, vomiting, behavioral symptoms before starting MTX were enquired. If features of stomach ache, nausea, vomiting, restlessness and irritability were absent a score 0 was given, for mild score of 1; moderate score of 2 and for severe score of 3 was given. For each individual MISS item pre, post and associative features were enquired. The above questions were enquired at each visit for at least 3 months for patients who got enrolled in last trimester of study. Methotrexate intolerance was considered if MISS was $\geq 6$. Informed consent was taken from patients and ethical committee of the hospital.

**Results:**
Out of 150 patients of RA on MTX, 21 (14%) were found to have MISS $\geq 6$. out of 21 patients 18 were on oral MTX and 3 were on parental MTX. 6 (4.9%) had stomach ache as anticipatory symptom on oral MTX and 3 (11.1%) on parental MTX. 18 (14.6%) on oral MTX were having stomach ache after MTX and in 11.1% after parental MTX (p 0.024). 12 (9.7%) of patients on oral MTX were having stomach ache as associative symptom, 3 (11.1%) on parental MTX were having stomach ache as associative symptom. 15 (12.2%) patients on oral MTX were having nausea as anticipatory symptom, 3 (11.1%) on parental MTX were having nausea as associative symptom, after MTX intake 31.7% of patients had nausea on oral MTX and 11.1% on parental MTX (p 0.019). 22.5% of patients were found to have nauseae as associative symptom on oral MTX, 11.1% were found to have nausea as associative symptom on parental MTX. 2.4% patients on oral MTX were found to have vomiting as anticipatory symptom. None on parental MTX were found to have vomiting as anticipatory symptom. 12.2% on oral MTX were having vomiting after MTX and 11.1% of patients were having vomiting after parental MTX. 2.4% patients on oral MTX were found to have restlessness after oral MTX and 11.1% were found to have restlessness after parental MTX. 9.8% of patients were found to have irritability after oral MTX(Table 1-14).

**Table 1:** Showing gender distribution of patients.

| sex   | route       | oral    | parenteral | total  |
|-------|-------------|---------|------------|--------|
| female| 93, 75.60%  | 27, 100.00% |           | 120, 80% |
| male  | 30, 24.40%  | 0, 0.00% |           | 30, 20.00% |
| total | 123, 100.00% | 27, 100.00% |           | 150, 100.00% |

**Table 2:** Showing number and percentage of RA patients experience anticipatory stomach ache 1 cell (25.0%) have expected less than 5; HH minimum expected is 1.62.

| route       | oral    | Parenteral | total  |
|-------------|---------|------------|--------|
| Nil (0)     | 117, 95.1% | 24, 88.9% | 141, 94.0% |
| Mild (1)    | 6, 4.9%  | 3, 11.1%   | 9, 6.0% |
| Total       | 123, 100.0% | 27, 100.0% | 150, 100.0% |

**Table 2a:** C computed only for a 2X2 table.

|                      | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
|----------------------|-------|----|-----------------------|----------------------|----------------------|
| Pearson ChiSquare    | 1.525 | a | 1.0                   | 0.217                |                      |
| Continuity Correction| 0.620 | 1 | 1.0                   | 0.431                |                      |
| Likelihood ratio     | 1.306 | 1 | 1.0                   | 0.253                |                      |
| Fisher’s Exact test  |       |   |                       |                      |                      |
| Linear-by-linear association | 1.515 | 1 | 1.0                   | 0.206                | 0.206                |
| N of valid cases     | 150   |   |                       |                      |                      |
Table 3: Showing number and percentage of patient having stomach ache after MTX.

| Route       | Oral (105) | Parenteral (24) | Total (129) |
|-------------|------------|-----------------|-------------|
| Nil (0)     | 85.4%      | 88.9%           | 86.0%       |
| Mild (1)    | 12.2%      | 0.0%            | 10%         |
| Moderate (2)| 2.4%       | 11.1%           | 6.4%        |
| Total       | 100%       | 100%            | 100%        |

Table 3a: Chi-Square Tests.

| Test Type                     | Value     | Df. | Asymp. Sig. (2-sided) |
|-------------------------------|-----------|-----|-----------------------|
| Pearson Chi-Square            | 7.487a    | 2   | .024                  |
| Likelihood ratio              | 9.147     | 2   | .010                  |
| Linear-by-linear association  | .256      | 1   | .613                  |
| N of valid cases              | 150       |     |                       |

Table 4: Showing number and percentage of patients having stomach ache as associative symptom.

| Route       | Oral (111) | Parenteral (24) | Total (132) |
|-------------|------------|-----------------|-------------|
| Nil (0)     | 90.2%      | 88.9%           | 88.0%       |
| Mild (1)    | 7.3%       | 11.1%           | 8.0%        |
| Moderate (2)| 0%         | 4.0%            | 4.0%        |
| Severe (3)  | 2.4%       | 0.0%            | 2.4%        |
| Total       | 100%       | 100%            | 100%        |

Table 4a: Chi-square test.

| Test Type                     | Value     | Df. | Asymp. Sig. (2-sided) |
|-------------------------------|-----------|-----|-----------------------|
| Pearson Chi-Square            | 1.061a    | 2   | .588                  |
| Likelihood ratio              | 1.560     | 2   | .458                  |
| Linear-by-linear association  | 114       | 1   | .736                  |
| N of valid cases              | 150       |     |                       |

Table 5: Showing number and percentage of patients having nausea as anticipatory symptom.

| Route       | Oral (108) | Parenteral (24) | Total (132) |
|-------------|------------|-----------------|-------------|
| Nil (0)     | 87.80%     | 88.90%          | 88.00%      |
| Mild (1)    | 9.80%      | 0.00%           | 8.00%       |
| Moderate (2)| 2.40%      | 11.10%          | 4.00%       |
| Total       | 100%       | 100%            | 100%        |

Table 5a: Chi-square test.

| Test Type                     | Value     | Df. | Asymp. Sig. (2-sided) |
|-------------------------------|-----------|-----|-----------------------|
| Pearson Chi-Square            | 6.800a    | 2   | .033                  |
| Likelihood ratio              | 7.928     | 2   | .019                  |
| Linear-by-linear association  | .591      | 1   | .442                  |
| N of valid cases              | 150       |     |                       |

Table 6: Showing number and percentage of patients having nausea after MTX intake.

| Route       | Oral (84) | Parenteral (24) | Total (108) |
|-------------|-----------|-----------------|-------------|
| Nil (0)     | 68.3%     | 88.9%           | 72.0%       |
| Mild (1)    | 18%       | 0               | 18%         |
| Route     | Total     | Oral % | Parenteral % | Total % |
|-----------|-----------|--------|--------------|---------|
| Nil (0)   | 117       | 93     | 24           | 79.6%   |
| Mild(1)   | 18        | 15     | 0            | 12.0%   |
| Moderate(2)| 9        | 6      | 3            | 6.1%    |
| Severe (3) | 3        | 3      | 0            | 2.0%    |
| Total     | 147       | 123.100%| 27.100%      | 100.0%  |

Table 7a: - 4 cells (50.0%) have expected less than 5. The minimum expected is 55.

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| Table 8a: - 2 cells (50.0%) have expected less than 5. The minimum expected is 54; Computed only for a 2X2 table
|------------------|--------|------------------|------------------|
|                  | value  | Df.  | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
| Pearson Chi-Square | 0.627a | 1    | .412                |                      |                      |
| Continuity correction | .004  | 1    | .952                |                      |                      |
| Likelihood ratio   | 1.204  | 1    | .273                |                      |                      |
| Fisher exact test  |        |      | 1.000               | 0.549                |
| Linear-by-linear association | .667 | 1    | .414                |                      |
| N of valid cases   | 150    |      |                     |                      |
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Table 9: Showing number and percentage of patients having vomiting after MTX intake.

| route      | oral  | parenteral | total     |     |
|------------|-------|------------|-----------|-----|
| Nil (0)    | 108   | 24         | 132       | 88.00%
| Mild(1)    | 64.9% | 311.1%     | 9.60%     |     |
| Moderate(2)| 9     | 0.0%       | 9         | 6.00%|
| total      | 123   | 27.100%    | 150       | 100% |

Table 9a: 2 cells (33.3%) have expected less than 5. The minimum expected is 1.62.

| value                  | Df. | Asymp. Sig. (2-sided) |        |        |       |
|------------------------|-----|-----------------------|--------|--------|-------|
| Pearson Chi-Square      | 3.412a | 2            | 0.182 |        |       |
| Likelihood ratio        | 4.788 | 2                          | .091 |        |       |
| Linear-by-linear association | .580 | 1                       | .449 |        |       |
| N of valid cases        | 150  |                          |        |        |       |

Table 10: Showing number and percentage of patients having restlessness after MTX intake.

| route      | oral  | parenteral | total     |     |
|------------|-------|------------|-----------|-----|
| Nil (0)    | 111   | 24         | 135       | 90.00%
| Mild(1)    | 12    | 3          | 15        | 10.00%
| total      | 123   | 27.100%    | 150       | 100% |

Table 10a: 1 cell (25.0%) has expected less than 5. The minimum expected is 2.70; Computed only for 2X2 table.

| value                  | Df. | Asymp. Sig. (2-sided) |        |        |       |
|------------------------|-----|-----------------------|--------|--------|-------|
| Pearson Chi-Square      | .045a | 1                  | .823 |        |       |
| Continuity correction   | 0.00 | 1                          | 1.000 |        |       |
| Likelihood ratio        | 0.004 | 1                     | .834 |        |       |
| Fisher exact test       |       |                       | 0.735 | 0.531 |       |
| Linear-by-linear association | .045 | 1                        | .832 |        |       |
| N of valid cases        | 150  |                          |        |        |       |

Table 11: Showing number and percentage of patients having irritability due to MTX intake.

| route      | oral  | parenteral | total     |     |
|------------|-------|------------|-----------|-----|
| Nil (0)    | 111   | 24         | 135       | 90.00%
| Mild(1)    | 12    | 3          | 15        | 10.00%
| total      | 123   | 27.100%    | 150       | 100% |

Table 11a: 1 cell (25.0%) has expected less than 5. The minimum expected is 2.70; Computed only for 2X2 table.

| value                  | Df. | Asymp. Sig. (2-sided) |        |        |       |
|------------------------|-----|-----------------------|--------|--------|-------|
| Pearson Chi-Square      | .045a | 1                  | .823 |        |       |
| Continuity correction   | 0.00 | 1                          | 1.000 |        |       |
| Likelihood ratio        | 0.004 | 1                     | .834 |        |       |
| Fisher exact test       |       |                       | 0.735 | 0.531 |       |
| Linear-by-linear association | .045 | 1                        | .832 |        |       |
| N of valid cases        | 150  |                          |        |        |       |
## Table 12: Depicting number of patients refusal to take MTX.

| route          | oral  | parenteral | total | nil (0) | 123 | 27 | 150 | 123.100% | 27.100% | 150,100% |
|----------------|-------|------------|-------|---------|------|----|-----|--------|---------|----------|

## Table 13: Showing number and percentage of patients taking drugs in addition to MTX.

| route | oral  | parenteral | total |
|-------|-------|------------|-------|
| Hcqs  | 81    | 18         | 99    |
| 65.9% | 66.7% | 66.0%      |
| Lefno | 3     | 3          | 6     |
| 2.4%  | 11.1% | 4.0%       |
| Mps   | 27    | 3          | 30    |
| 22.0% | 11.1% | 20.0%      |
| Ssz   | 12    | 3          | 15    |
| 9.8%  | 11.1% | 10.0%      |
| total | 123   | 27         | 150   |
| 100.0%| 100.0%| 100.0%     |

### Table 13 a): 3 cells (37.5%) have expected less than 5. The minimum expected is 1.08.

| value           | Df. | Asymp. Sig. (2-sided) |
|-----------------|-----|-----------------------|
| Pearson Chi-Square | 5.506a | 3            | .138       |
| Likelihood ratio  | 4.704  | 4            | .195       |
| N of valid cases | 150  |             |            |

## Table 14: Showing minimum to maximum MISS (0-9).

| Score | oral  | parenteral | total |
|-------|-------|------------|-------|
| 0     | 81    | 21         | 102   |
| 65.9% | 77.8% |            | 68.0% |
| 1     | 3     | 0          | 3     |
| 2.4%  | 0.0%  |            | 2.0%  |
| 2     | 6     | 3          | 6     |
| 6.49% | 0.0%  |            | 4.0%  |
| 3     | 9     | 3          | 12    |
| 9.73% | 11.1% |            | 8.0%  |
| 4     | 6     | 0          | 6     |
| 6.49% | 0.0%  |            | 4.0%  |
| 6     | 9     | 0          | 9     |
| 7.3%  | 0.0%  |            | 6.0%  |
| 7     | 3     | 0          | 3     |
| 3.24% | 0.0%  |            | 3.2%  |
| 9     | 6     | 3          | 9     |
| 4.9%  | 11.1% |            | 6.0%  |
| total | 123   | 27         | 150   |
| 100.0%| 100.0%|            | 100.0%|

### Table 14 a): 11 cells (68.8%) have expected less than 5. The minimum expected is 54.

| value           | Df. | Asymp. Sig. (2-sided) |
|-----------------|-----|-----------------------|
| Pearson Chi-Square | 8.222a | 7            | .313       |
| Likelihood ratio  | 12.7414 | 7            | .079       |
| Linear by linear association | .195  | 1            | .659       |
| N of valid cases | 150  |            |            |
Discussion:
MTX was found in 21(14%) RA patients in our study compared to 10.4% of 249 patients of RA seen in a study by BulatovicCalasan, et al. [8]. 14.4% on oral MTX were having MISS ≥ 6 as compared to 11.1% on parental MTX in our study. It was more on parental than on oral MTX in the study conducted by BulatovicCalasan, et al. (20.6 Vs. 6.2%) [8]. In our study, 31.7% patients on oral MTX and 11.1% on parental MTX were having nausea after MTX intake. In the study conducted by BulatovicCalasan, et al. 32% was found to have nausea. It was found in 14.4-28% in the study conducted by Jacobs, et al. and were having gastrointestinal symptoms and behavioural symptoms though not qualifying MISS ≥ 6. Keeping the usefulness of MTX and mitigation by various procedures in view use of MISS is recommended to apply for patients of RA on MTX. The mitigation procedures include change of route of MTX administration, folic acid administration, antiemetic and behavioral therapy (Tables 7-14) [11,12].

Conclusion:
Application of MISS reveals that in addition to known gastrointestinal symptoms including abdominal pain, nausea, vomiting after MTX therapy, anticipatory and associative features which are believed to be conditioned phenomenon could hamper MTX compliance. Timely intervention like change of route, folic acid, antiemetic, behavioral therapy can prevent the MTX incompliance and provide a smooth path for an otherwise effective DMARD for RA.

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