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Prevalence of MTX Intolerance in Rheumatoid Arthritis- A 3 Year Prospective Hospital Based Study

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Abstract

Background: Rheumatoid arthritis is most common inflammatory arthritis. Methotrexate is backbone of treatment regimens.

Objective: To determine the prevalence of Methotrexate intolerance in rheumatoid arthritis.

Material and Methods: 150 patients of RA including 120 females and 30 males attending rheumatology services of hospital from December 2012 to December 2015 were prescribed MTX as per approved protocol and were followed for Methotrexate Intolerance Severity Score (MISS).

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

Conclusion: MISS is an important tool for application in RA to know Methotrexate intolerance and timely intervention to mitigate the same in order to prevent the incompliance of an otherwise very effective DMARD for RA.

Keywords: Methotrexate (MTX); Methotrexate Intolerance Severity Score (MISS); Rheumatoid Arthritis (RA)

Introduction

RA is the most common inflammatory arthritis affecting 0.5-1% of the global population [1-3]. If not treated in time and adequately can lead to various deformities particularly to hands. After the introduction of DMARDS including MTX deformities like swan neck, z deformity and boutonniere deformities are no longer seen now. MTX is the backbone of almost all combination treatment regimens of RA and has resulted in enhanced efficacy over MTX alone, without added increases in side effects [4-7]. To improve its compliance MTX intolerance parameters are looked for and required mitigating actions taken to improve its compliance.

Materials and Methods

150 patients of RA including 120 females and 30 males attending Rheumatology services of hospital from December 2012 to December 2015 were prescribed MTX as per approved standard and were followed for MTX intolerance as per validated Methotrexate intolerance severity score questionnaire. MTX intolerance features were enquired at each visit which was of 4-6 weekly. Base line stomach ache, nausea, vomiting, behavioural 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 ≥ 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 ≥ 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 nausea 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. 12 (9.8%) 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 (Tables 1-6).

Sex	Route		Total
	Oral	Parentral	
Female	93 75.60%	27 100.00%	120 80.00%
Male	30 24.40%	0 0.00%	30 20.00%
Total	123 100.00%	27 100.00%	150 100.00%

Table 1: Showing gender distribution of patients.

	Route		Total
	Oral	Parentral	
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 2: Showing number and percentage of RA patients experience anticipatory stomach ache 1 cell (25.0%) have expected less than 5; The minimum expected is 1.62.

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-s9ided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.525a	1	0.217		
Continuity Correctionb	0.620	1	0.431		
Likelihood ratio	1.306	1	0.253		
Fisher's Exact test				0.206	0.206
Linear-by-linear association	1.515	1	0.218		
N of valid cases	150				

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

	Route		Total
	Oral	Parentral	
Nil (0)	105 85.4%	24 88.9%	129 86.0%
Mild (1)	15 12.2%	0 0.0%	15 10%
Moderate (2)	3 2.4%	3 11.1%	6 4%
Total	123	27	150
	100%	100%	100%

Table 3: Showing number and percentage of patient having stomach ache after MTX.

	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 3a: Chi-Square Tests.

	Route		Total
	Oral	Parentral	
Nil (0)	111 90.2%	24 88.9%	135 90.0%
Mild (1)	9 7.3%	3 11.1%	12 8.0%
Severe (3)	3 2.4%	0 0.0%	3 2.0%
Total	123 100.0%	27 100.0%	150 100.0%

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

	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 4a: 3 cells (50.0%) have expected less than 5. The minimum expected is 54.

	Route		Total
	Oral	Parentral	
Nil (0)	108 87.80%	24 88.90%	132 88.00%
Mild (1)	12 9.80%	0 0.00%	12 8.00%
Moderate (2)	3 2.40%	3 11.10%	6 4.00%
Total	123	27	150

	100.00%	100.00%	100.00%

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

	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 5a): 3 cells (50.0%) have expected less than 5. The minimum expected is 1.08.

	Route		Total
	Oral	Parentral	
Nil (0)	84 68.3%	24 88.9%	108 72.0%
Mild (1)	18 14.6%	0 0.0%	18 12.0%
Moderate (2)	15 12.2%	0 0.0%	15 10.0%
Severe (3)	6 4.9%	3 11.1%	9 6.0%
Total	123 100.0%	27 100.0%	150 100.0%

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

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	9.982a	3	.019
Likelihood ratio	15.544	3	.001
Linear-by-linear association	1.122	1	.290
N of valid cases	150		

Table 6a): Chi-Square Tests.

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 Bulatovic Calasan, 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 Bulatovic Calasan, 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 Bulatovic Calasan, et al. 32% was found to have nausea. It was found in 14.4-28% in the study conducted by Jacobs, et al. and Kremer et al. [9,10]. 19.5% of RA on oral and 11.1% on parental MTX 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 behavioural therapy (Tables 7-14) [11,12].

	Route		Total
	Oral	Parentral	
Nil (0)	93 77.5%	24 88.9%	117 79.6%
Mild (1)	18 15.0%	0 0.0%	18 12.2%
Moderate (2)	6 5.0%	3 11.1%	9 6.1%
Severe (3)	3 2.5%	0 0.0%	3 2.0%
Total	120 100.0%	27 100.0%	147 100.0%

Table 7: Showing number and percentage of patients having nausea as associative symptom.

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6.429a	3	.093
Likelihood ratio	10.018	3	.018
Linear-by-linear association	.506	1	.477
N of valid cases	147		

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

	Route		Total
	Oral	Parentral	
Nil (0)	120 97.6%	27 100.0%	147 98.0%
Mild (2)	3 2.4%	0 0.0%	3 2.0%
Total	123 100.0%	27 100.0%	150 100.0%

Table 8: Showing number and percentage of patients having vomiting as anticipatory symptom.

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)

Pearson Chi-Square	.627a	1	.412		
Continuity correction	.004	1	.952		
Likelihood ratio	1.204	1	.273		
Fisher's exact test				1.000	.549
Linear-by-linear association	.667	1	.414		
N of valid cases	150				

Table 8a: 2 cells (50.0%) have expected less than 5 the minimum expected is 54; Computed only for a 2X2 table.

	Route		Total
	Oral	**Parentral**	
Nil (0)	108 87.8%	24 88.9%	132 88.0%
Mild (1)	6 4.9%	3 11.1%	9 6.0%
Moderate (2)	9 7.3%	0 0.0%	9 6.0%
Total	123 100.0%	27 100.0%	150 100.0%

Table 9: Showing number and percentage of patients having vomiting after MTX intake.

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

	Route		Total
	Oral	**Parentral**	
Nil (0)	111 90.2%	24 88.9%	135 90.0%
Mild (2)	12 9.8%	3 11.1%	15 10.0%
Total	123	27	150

	100.0%	100.0%	100.0%

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

	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	.045a	1	.823		
Continuity correction Likelihood ratio	.000 .044	1 1	1.000 .834		
Fisher's exact test				.735	.531
Linear-by-linear association	.045	1	.832		
N of valid cases	150				

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

	Route		Total
	Oral	**Parentral**	
Nil (0)	111 90.2%	24 88.9%	135 90.0%
Mild (1)	12 9.8%	3 11.1%	15 10.0%
Total	123 100.0%	27 100.0%	150 100.0%

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

	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	.045	1	.832		
Continuity correction	.000	1	1.000		
Likelihood ratio	.044	1	.834		
Fisher's exact test				.735	.531
Linear-by-linear association	.045	1	.832		
N of valid cases	150				

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

Oral **Parentral** **Total**	**Route**		**Total**
Nil (0)	123	27	150

	100.0%	100.0%	100.0%
Total	123 100.0%	27 100.0%	150 100.0%

Table 12: Depicting number of patients refusal to take MTX.

	Route		**Total**
	Oral	**Parentral**	
hcqs	81 65.9%	18 66.7%	99 66.0%
lefno	3 2.4%	3 11.1%	6 4.0%
Mps	27 22.0%	3 11.1%	30 20.0%
ssz	12 9.8%	3 11.1%	15 10.0%
Total	123 100.0%	27 100.0%	150 100.0%

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

	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	5.506a	3	.138
Likelihood ratio	4.704	3	.195
N of valid cases	150		

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

	Route		**Total**
	Oral	**Parentral**	
0	81 65.9%	21 77.8	102 68.0%
1	3 2.4%	0 0.0	3 2.0%
2	6 4.9%	0 0.0	6 4.0%
3	9 7.3%	3 11.1%	12 8.0%
4	6 4.9%	0 0.0	6 4.0%
6	9 7.3%	0 0.0%	9 6.0%
7	3	0	3
	2.4%	0.0%	2.0%
9	6 4.9%	3 11.1%	9 6.0%
Total score	123 100.0%	27 100.0%	150 100.0%

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

	Value	**Df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	8.222a	7	.313
Likelihood ratio	12.741	7	.079
Linear-by-linear association	.195	1	.659
N of valid cases	150		

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

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, behavioural therapy can prevent the MTX incompliance and provide a smooth path for an otherwise effective DMARD for RA.

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