Patterns of Oral and Subcutaneous Methotrexate Use among Rheumatoid Arthritis Patients Enrolled in the U.S. Medicare Program

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Background

- Methotrexate (MTX) is an anchor medication for the treatment of rheumatoid arthritis (RA) and other inflammatory conditions
- It remains the first-line medication for newly diagnosed RA
- Biologics in combination with MTX produce significantly greater clinical response than biologics alone
- MTX can be given orally, subcutaneously, or via intramuscular injection. Bioavailabiity varies significantly when given orally
  - 21% to 96% of MTX taken orally is bioavailable
  - Varies more with larger MTX doses
- Different strategies exist to manage patients with insufficient response to MTX monotherapy before initiating biologics
  - Switching to subcutaneous (SC) MTX
  - Titrating to higher oral MTX doses
  - Adding or switching to a different non-biologic disease modifying anti-rheumatic drugs (DMARDs)

Objectives

- To examine the use of MTX among RA patients initiating MTX monotherapy, with focus on MTX mean dose, peak dose, and method of administration
- To explore the likelihood of starting a biologic in relation to switching to SC MTX, titrating to higher doses of oral MTX, or adding/switching to hydroxycholoroquine (HCQ), sulfasalazine (SSZ), or leflunomide (LEF)

Methods

- Study Population
  - RA patients enrolled in fee-for-service Medicare, 2006-2010
  - New users of oral MTX monotherapy,
  - Baseline period of 6 months of continuous coverage prior to first MTX use, with
    - At least two RA diagnosis codes from rheumatologist
    - No filled prescription of MTX, HCQ, SSZ, LEF, or any biologic
- Retrospective cohort study
  - Follow-up started at time of MTX initiation
  - Follow-up ended when patient lost coverage, died, or by December 31, 2010

Methods cont.

Covariates and exposures

- Patient baseline characteristics (demographic and clinical)
- Methotrexate use
  - Starting dose, average dose, peak dose
  - MTX use during entire follow-up and MTX use immediately prior to biologic initiation (among subgroup who used biologics)
  - MTX persistence: Discontinuation defined as gap > 90 days

Analytical outcomes of interest

- Time to initiation of biologic
- Compared switching to SC MTX with:
  - Titrating to higher oral MTX doses, defined as an increase of 2.5 mg or more from prior MTX dose (referent)
  - Switching to or adding HCQ
  - Switching to or adding SSZ
  - Switching to or adding LEF
- Statistical analysis
  - Mean and standard deviation (std), median and inter-quartile range (IQR), number and percent (%) for descriptive outcomes
  - Kaplan Meier for persistence on MTX monotherapy
  - Time-varying COX regression for time to biologic initiation
    - Among patients who subsequently increased oral MTX doses, switched to SC MTX, or switched to or added HCQ, SSZ, or LEF
    - Adjusting for age, sex, original reason for Medicare enrollment, receipt of state subsidy, use of oral glucocorticoids, NSAIDs, and narcotics, inpatient and outpatient visit during baseline, and previous dose of oral MTX

Results

- We identified 20,406 eligible RA patients as new users of MTX monotherapy
  - Mean (std) age 70 (11) years
  - 77% were women
  - During baseline, 61.5% patients used oral glucocorticoids, 34.1% NSAIDs, and 60.8% narcotics

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Table 1. Methotrexate Use among Rheumatoid Arthritis Patients enrolled in Medicare (n=20,406)

Starting dose, mg/week (mean, std)	13.1 (8.7)
All MTX prescriptions combined, %	
<10	16.1%
≥10 and <15	32.9%
≥15 and <20	28.1%
≥20	23.0%
Peak MTX anytime during follow-up, %	
<10	10.0%
≥10 and <15	22.8%
≥15 and <20	22.7%
≥20	44.5%
% of patients who initiated a biologic	19.1%
Among patients who initiated a biologic (subgroup of entire cohort)	
Peak MTX before initiating biologic, %	
<15	21.7%
≥15 and <20	22.8%
≥20	55.5%
Treatment change before initiating biologics, %	
Stayed only on oral MTX	75.8%
Switched to SC MTX	3.9%
Added or switched to HCQ	11.9%
Added or switched to SSQ	5.0%
Added or switched to LEF	9.3%
Initiated anti-TNF biologic (rather than non-TNF biologic)	84.7%

Table 2. Multivariable adjusted* associations with initiation of biologic among RA patients with treatment changes prior to biologic initiation (n=12,652)

Treatment strategies	Hazard Ratio**
Add/switch to LEF	0.90 (0.62-1.32)
Add/switch to SSZ	0.91 (0.61-1.37)
Increased oral MTX dose	0.81 (0.61-1.09)
Add/switch to HCQ	0.56 (0.39-0.81)
Switch to SC MTX	1.0 (Reference)

*Adjusting for age, gender, original reason for Medicare enrollment, receipt of state subsidy, use of oral glucocorticoids, NSAIDs, and narcotics, inpatient and outpatient visit during baseline, and dose of oral MTX

** Hazard ratio comparing various treatment strategies to SC MTX

Results, Continued

- Features of MTX use
  - Average starting dose 13.1 mg/week
  - Most commonly used MTX doses during follow-up was between 10 and 15 mg/week
  - During follow-up
    - 10% patients only used a dose <10 mg/week
    - 32.2% never used a dose higher than 15 mg/week
    - 44.5% used a dose higher than 20 mg/week
    - 38.0% never changed doses of MTX
  - Among patients who initiated a biologic, and prior to starting,
    - 44.5% never used MTX at >= 20 mg/week
    - 21.7%% never used MTX at >= 15 mg/week
    - 75.8% stayed on oral MTX (with or without dose change)
    - 11.9% switched or added HCQ
    - 5.0% switched or added SSZ
    - 9.3% switched or added LEF
    - 3.9% switched to SC MTX
- At one year, approximately 50% of the patients remained on MTX monotherapy
- In multivariable models
  - Compared to add/switch to HCQ, SQ MTX use associated with a higher likelihood of initiating a biologic
  - No difference between SQ MTX and other treatment strategies
- Limitations of the study
  - Lack of clinical data
    - Unable to adjust for disease severity and activity. This likely explains the 'protective' effect of patients using HCQ, in that less severe patients were given this treatment compared to more potent RA treatments
  - Despite new MTX user design, unable to confirm with certainty patients had recent onset RA

Conclusions

- Use of SC MTX and higher doses of oral MTX was relatively uncommon among RA patients enrolled in Medicare
  - More than half of patients never used MTX at 20 mg/week or more
  - Even among patients who went on to initiate a biologic, 44% never used MTX at >= 20 mg/week
- MTX treatment may not be optimized in routine RA care in general, especially before biologics are initiated