Incidence Rate of Biologic/Targeted Synthetic (b/ts) Disease Modifying Antirheumatic Drugs (DMARDs) for Rheumatoid Arthritis (RA), Preceding Therapy and Time to Discontinuation in a Commercially Insured Population

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Background

- Rheumatoid Arthritis (RA) guidelines recommend:[1,2]
  - Disease modifying antirheumatic (DMARD) therapy should be started as soon as the RA diagnosis is made, and
  - A "treat-to-target" strategy should be used that includes frequent evaluation using structured RA disease activity measures to guide treatment adjustments that may include conventional synthetic (cs) DMARDs and escalation of some patients to biologic/targeted synthetic (b/ts) DMARDs.
- A study[3] using the same population as this report found, among all RA members:
  - About one-third had a 2016 b/tsDMARD claim with b/tsDMARDs costs accounting for more than two-thirds of the total RA direct medical plus pharmacy costs.
  - Almost one-third had no 2016 claim for either a csDMARD or a b/tsDMARD.
- Methotrexate (MTX) monotherapy is recommended as first line therapy for RA, but many patients do not achieve remission or low disease activity on MTX alone.
  - The decision to immediately escalate therapy for such patients to a b/tsDMARD is now common practice.
  - Two large recently published clinical trials of RA patients with active disease despite MTX, found triple csDMARD therapy as second line therapy, defined as MTX + hydroxychloroquine (HCQ) + sulfasalazine (SSZ) was substantially more cost-effective than immediate biologic DMARD escalation.[4,5,6,7]

Objective

To determine, in a commercially insured population, the:

- Incidence rate of new RA diagnosis and the percentage of members with newly diagnosed RA who initiated any DMARD therapy within two years of diagnosis;
- b/tsDMARD new therapy initiation rate;
- csDMARDs use in the year preceding b/tsDMARD therapy initiation; and
- Time to b/tsDMARD therapy discontinuation stratified by the number of different agents used in sequence.

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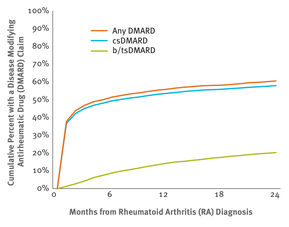
Methods

- In 2016, 15 million members were queried to identify members continuously enrolled from 2013 through 2016 (four years) and age 18 to 64 years on Dec. 31, 2016. Members were categorized as having RA if:
  - They had two or more medical claims occurring at least two months apart with a diagnosis code for RA, and
  - Their total number of different claim dates with a diagnosis code for RA was greater than the total number of claim dates for the member for any other autoimmune disease.
- New RA diagnosis incidence was determined for calendar year 2014. This was defined as the number of study members with RA whose first medical claim with a diagnosis code for RA was incurred in 2014, excluding members with any DMARD claim in 2013. For all members with a new diagnosis of RA in 2014, complete pharmacy and medical claims were available for at least the next two years, which were used to determine how many members had a DMARD claim within two years of diagnosis.
- All pharmacy and medical drug claims for RA members were analyzed to determine the first incurred date (index date), if any, for a:
  - csDMARD, defined as MTX, HCQ, SSZ or leflunomide (LEF).
  - b/tsDMARD, defined as etanercept (Enbrel®), adalimumab (Humira®), abatacept (Orencia®), infliximab (Remicade® or Inflectra®), rituximab (Rituxan® coded for RA), tocilizumab (Actemra®), certolizumab (Cimzia®), golimumab (Simponi® or Simponi Aria®), anakinra (Kineret®) or tofacitinib (Xeljanz®).
- Days covered by DMARDs were determined:
  - For pharmacy claims, from claim dates and days supply.
  - For medical claims, from claim dates and the lesser of the observed intervals between claims and the recommended dosing interval for medical claims.
- Time to first discontinuation of b/tsDMARD therapy initiated in calendar year 2014 was described using Kaplan-Meier analysis and defining discontinuation as a gap >= days supply of the last claim plus 60 days (e.g., a gap of at least 90 days for most pharmacy claims, which are typically dispensed as four weeks supplies of drug) in b/tsDMARD therapy, irrespective of agents (i.e., members switched from one b/tsDMARD to another were regarded as continuing therapy if there was a coverage gap of less than 60 days). All members had at least two years of claims follow-up.
  - An unstratified analysis was performed for all members who initiated b/tsDMARD therapy.
  - A second analysis stratified members into two groups: those who used only a single agent and those who switched to different agents, one or more times.
- A substantial majority in this analysis were subject to utilization management policies related to b/tsDMARDs such as prior authorization requirements for new starts. However, the researcher did not have detailed information about which claims were subject to what requirements or to any results from utilization management processes such as what information was specified by the provider.

Results

- In 2016 there was an average of 13.91 million members per month younger than 65 years, of whom 3.25 million were continuously enrolled from 2013 through 2016 and age 18 to 64 years old. Of these 3.25 million, 26,098 were categorized as having an RA diagnosis, for an RA prevalence of 741 (0.74%) per 100,000 members 18 to 64 years old total, 1,123 (1.12%) of females and 354 (0.35%) of males.
- Of the 26,098 members with RA, 2,414 had their first medical claim with a diagnosis code for RA in 2014, for a RA incidence rate of 69 (0.07%) per 100,000 per year total, 101 (0.10%) of females and 38 (0.04%) of males. These findings closely match those of another administrative claims study[8] but are higher than the incidence rate found from analysis of an electronic medical record databases.[9]
- The time between first RA diagnosis and first DMARD claim is shown in **Figure 1** for the 2,414 members with first RA diagnosis in 2014:
  - 912 (37.8%) had a claim for any DMARD within one month of diagnosis, 1,350 (55.9%) within 12 months, and 1,463 (60.6%) within 24 months.
  - 31 (1.3%) had a claim for a b/tsDMARD within one month of diagnosis, 345 (14.3%) within 12 months, and 489 (20.3%) within 24 months.
- Of the 26,098 members with RA, 10,143 (38.9%) had a claim for a b/tsDMARD between Jan. 1, 2013 and Dec. 31, 2016. Of the 10,143 members:
  - 6,347 (62.6%) had their first b/tsDMARD claim in 2013; limited to less than 12 months of claims history.
  - 3,796 of 10,143 (37.4%) had their first b/tsDMARD claim >=Jan. 1, 2014, for an incidence rate of new initiation of 35.9 per year per 100,000 members age 18 to 64.
- **Table 1** shows the number of members who had any days covered by a csDMARD in the 12 months preceding newly initiation of a b/tsDMARD.
  - 455 of 3,796 (12.0%) had no claim for a csDMARD,
  - 1,384 (36.5%) had MTX monotherapy,
  - 443 (11.7%) had another monotherapy,
  - 1,173 (30.9%) had two csDMARDs, and
  - 331 (8.7%) had three csDMARDs, of whom 192 (5.1%) used MTX+HCQ+SSZ or all four csDMARDs.
- Of the 9,135 members who had a csDMARD claim in 2016:
  - 3,137 (34.3%) of these members used MTX monotherapy,
  - 2,511 (27.5%) HCQ monotherapy,
  - 1,355 (14.8%) MTX+HCQ two-drug therapy, and
  - 389 (4.3%) had three csDMARDs, of whom 240 (2.6%) used MTX+HCQ+SSZ or all four csDMARDs.
- Of the 1,245 members initiating b/tsDMARD therapy in 2016:
  - 83 (6.7%) had no previous claim for a csDMARD in >= three years prior;
  - 135 (11.6%) had b/tsDMARD index date less than 12 weeks after their first claim for a csDMARD; and
  - 303 (26.1%) had b/tsDMARD index date less than 24 weeks after their first claim for a csDMARD.
- Time to b/tsDMARD discontinuation, for the 1,316 members initiating a b/tsDMARD in 2014:
  - **Figure 2a** shows 27.9% had discontinued b/tsDMARDs by 6 months, 43.1% by 12 months and 58.1% by 24 months.
  - **Figure 2b** shows 334 of the 1,316 (25.4%) switched one or more times to a different b/tsDMARD. 35.9% of these members had discontinued therapy by 24 months compared with 65.7% of the 982 of 1,316 (74.6%) who did not switch. The difference between these strata was significant (log rank chi square 107.8 [p<0.0001]).
  - These rates of discontinuation are somewhat higher than described in a recent meta-analysis of studies of tumor necrosis factor (TNF) inhibitors.

Figure 1. Time to First Disease Modifying Antirheumatic Drug (DMARD) Claim among 2,414 Members Newly Diagnosed with Rheumatoid Arthritis (RA) in 2014



csDMARD = conventional synthetic DMARD (see Methods for drug list), b/tsDMARD = biologic or targeted synthetic DMARD (see Methods for drug list)

All 2,414 members were continuously enrolled from 2013 through 2016 with RA medical claims in 2014 and no medical RA claims or DMARD pharmacy claims in 2013

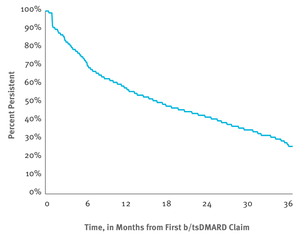
Table 1. Prior Conventional Synthetic (cs) Disease Modifying Antirheumatic Drug (DMARD) Therapy among 3,796 Members with Rheumatoid Arthritis (RA) Newly Initiating Biologic/ Targeted Synthetic (b/ts) DMARD

csDMARD Use in 12 Months Prior to New Start b/tsDMARD	Year of First b/tsDMARD (new start)							
	2014 N	2015 N	2016 N	Total N	2014 %	2015 %	2016 %	Total %
None	184	151	120	455	14.0%	12.2%	9.6%	12.0%
MTX	495	436	453	1,384	37.6%	35.3%	36.4%	36.5%
HCQ	65	62	70	197	4.9%	5.0%	5.6%	5.2%
LEF	51	62	58	171	3.9%	5.0%	4.7%	4.5%
SSZ	29	26	20	75	2.2%	2.1%	1.6%	2.0%
MTX+HCQ	193	229	231	653	14.7%	18.5%	18.6%	17.2%
MTX+LEF	57	42	64	163	4.3%	3.4%	5.1%	4.3%
MTX+SSZ	65	50	41	156	4.9%	4.0%	3.3%	4.1%
HCQ+LEF	34	31	42	107	2.6%	2.5%	3.4%	2.8%
HCQ+SSZ	16	19	30	65	1.2%	1.5%	2.4%	1.7%
SSZ+LEF	14	7	8	29	1.1%	0.6%	0.6%	0.8%
MTX+HCQ+SSZ	55	56	51	162	4.2%	4.5%	4.1%	4.3%
MTX+HCQ+LEF	35	38	35	108	2.7%	3.1%	2.8%	2.8%
MTX+SSZ+LEF	8	8	6	22	0.6%	0.6%	0.5%	0.6%
HCQ+SSZ+LEF	4	9	6	19	0.3%	0.7%	0.5%	0.5%
MTX+HCQ+SSZ+LEF	11	9	10	30	0.8%	0.7%	0.8%	0.8%
Total	**1,316**	**1,235**	**1,245**	**3,796**	**100.0%**	**100.0%**	**100.0%**	**100.0%**
Any MTX	919	868	891	2,678	69.8%	70.3%	71.6%	70.5%
Any HCQ	413	453	475	1,341	31.4%	36.7%	38.2%	35.3%
Any LEF	214	206	229	649	16.3%	16.7%	18.4%	17.1%
Any SSZ	202	184	172	558	15.3%	14.9%	13.8%	14.7%
No DMARD	184	151	120	455	14.0%	12.2%	9.6%	12.0%
csDMARD monotherapy	640	586	601	1,827	48.6%	47.4%	48.3%	48.1%
Two csDMARDs	379	378	416	1,173	28.8%	30.6%	33.4%	30.9%
>= three csDMARDs	113	120	108	341	8.6%	9.7%	8.7%	9.0%

csDMARD = conventional synthetic DMARD defined as MTX = methotrexate, HCQ = hydroxychloroquine, LEF = leflunomide, SSZ = sulfasalazine, b/tsDMARD = biologic or targeted synthetic DMARD (see Methods for drug list)

All 3,796 members were continuously enrolled from 2013 through 2016 with RA diagnosis medical claims

Figure 2a. Biologic/Targeted Synthetic Disease Modifying Antirheumatic Drug (b/tsDMARD) Kaplan-Meier Derived Persistency among 1,316 Members with Rheumatoid Arthritis (RA) Newly Initiating a b/tsDMARD in 2014



Members at risk*:

1,316	949	749	632	551	290	44

Discontinuation was defined as a 90 day gap in therapy from the end of a b/tsDMARD claim plus days supply and the next b/tsDMARD claim, allowing for switching to a different b/tsDMARD. For example, if an etanercept claim was incurred on Jan. 1, 2014 with a 30 days supply, then discontinuation would be declared if the member had no subsequent claim by May 1, 2014 (Jan. 1, 2014 + 30 days supply + 90 day gap).

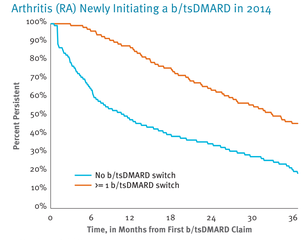
Eligibility: 1,316 members in this graph were commercially insured, continuously enrolled from 2013 through 2016, and less than 65 years of age as of Dec. 31, 2014 with at least one b/tsDMARD claim from during 2014 and an RA diagnosis

Censoring occurred when a member had a b/tsDMARD supply on Dec. 31, 2016 or less than 90 day gap in therapy during follow-up

*Members at risk: Members who did not discontinue therapy and were not censored up to and including the time point shown on the graph are at risk of discontinuing therapy or being censored in the future

All 1,316 members were continuously enrolled from 2013 through 2016 with RA medical claims in 2014 and no b/tsDMARD pharmacy claims in 2013

Figure 2b. Stratified by No Switch or Biologic/Targeted Synthetic Disease Modifying Antirheumatic Drug (b/tsDMARD) Switching — Kaplan-Meier Derived Persistency among 1,316 Members with Rheumatoid Arthritis (RA) Newly Initiating a b/tsDMARD in 2014



Members at risk*:

1:	982	627	462	386	337	165	0
2:	334	322	287	246	214	125	0

Discontinuation was defined as a 90 day gap in therapy from the end of a b/tsDMARD claim plus days supply and the next b/tsDMARD claim, stratified by if the member switched at any time to a different b/tsDMARD or there were no subsequent claims for alternative b/tsDMARD. For example, if an etanercept claim was incurred on Jan. 1, 2014 with a 30 days supply, then discontinuation would be declared if the member had no subsequent claim by May 1, 2014 (Jan. 1, 2014 + 30 days supply + 90 day gap).

Eligibility: 1,316 members in this graph were commercially insured, continuously enrolled from 2013 through 2016, and less than 65 years of age as of Dec. 31, 2014 with at least one b/tsDMARD claim from during 2014 and an RA diagnosis

Censoring occurred when a member had a b/tsDMARD supply on Dec. 31, 2016 or less than 90 day gap in therapy during follow-up

*Members at risk: Members who did not discontinue therapy and were not censored up to and including the time point shown on the graph are at risk of discontinuing therapy or being censored in the future

All 1,316 members were continuously enrolled from 2013 through 2016 with RA medical claims in 2014 and no b/tsDMARD pharmacy claims in 2013

Limitations

- As this study relies completely on administrative claims data some members may be misclassified as carrying a diagnosis of RA and for some members identified as having RA, the RA diagnosis assignment may be inaccurate.
- Use of csDMARDs prior to initiation of b/tsDMARD therapy was measured as any days covered during the preceding 12 months and probably overestimates the percentage of members with concurrent use of two or three different csDMARDs.
- Some members who discontinue b/tsDMARD therapy may subsequently re-start therapy. The frequency of this was not quantified in this analysis.

Conclusions

- This study found almost half of members newly diagnosed with RA did not have a DMARD claim within 12 months of diagnosis and almost 40% did not within 24 months. Managed care interventions that address this apparent gap in care could benefit these members.
- One in eight members newly initiating a b/tsDMARD had no csDMARD claim in the preceding 12 months even though a substantial majority of members were subject to a utilization management policy requiring prior use of a csDMARD. There was a 31% decrease in the lack of csDMARD prior to b/tsDMARD from 2014 to 2016, indicating improved prescribing in accordance with RA guidelines.
- Of concern was the finding that 12% of members initiated on a csDMARD escalated to a b/tsDMARD within 12 weeks of starting their csDMARD, which is inconsistent with the RA guidelines that recommend a 12 or more week csDMARD trial. In addition, more than 25% initiated b/tsDMARD therapy less than 24 weeks after their first claim for a csDMARD therapy, which would appear to be insufficient time for even one adjustment of the csDMARD regimen.
- The validated cost effective triple csDMARD therapy, defined as MTX+HCQ+SSZ, was found to be rarely attempted, at only 5%, in the 12 months prior to b/tsDMARD new start.
- b/tsDMARD therapy was frequently discontinued with 43% of members having discontinued within one year and 58% within two years. Although the reason for discontinuation is unknown, this high discontinuation rate indicates there is substantial waste occurring as the monthly b/tsDMARD drug cost is over $3,000.
- About 25% of those initiating b/tsDMARD therapy in 2014 switched one or more times to different b/tsDMARDs during follow-up. This subset had a significantly larger percentage with persistence to at least 24 months: 66% versus 36% of those who never switched. This apparent improvement in therapy may be the result of more careful monitoring and adjustment of therapy by some providers.
- Because of the high b/tsDMARDs cost and response variability to individual agents, initiating, discontinuing or switching therapy are critical decisions from the perspectives of drug costs and potential indirect RA costs. Health plans should evaluate whether their utilization management strategies encourage compliance with RA guideline recommendations and use of the most cost-effective triple csDMARD therapy.

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