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Changes in co-therapies after initiation of disease-modifying anti-rheumatic drugs (DMARDs) therapy in patients with rheumatoid arthritis

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Abstract

Objectives—We hypothesized that initiation of a new disease modifying anti-rheumatic drug DMARD) for rheumatoid arthritis (RA) treatment would decrease use of corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotics.

Methods—Using administrative databases we assembled 4 retrospective cohorts of RA patients (1998-2005), and identified 5 groups initiating DMARD regimens: methotrexate with (new MTX) or without (first MTX) use of other non-biologic DMARDs in the previous year; new hydroxychloroquine and/or sulfasalazine (new HCQ/SSZ) and new leflunomide (new LEF), both with previous use of MTX; and new TNF-α antagonists (new anti-TNF). We compared within-person differences in any use of co-therapies (≥1 prescription) between the 6 months before and the 6-12 months after DMARD initiation.

Results—Among 32476 DMARD initiators, the prevalence of corticosteroids, NSAIDs and narcotics use increased by 15%, 5% and 6% respectively in the 6 months before initiation compared to the previous 6 months suggesting worsening of the disease. In the 6 to 12 months after initiation for most initiator groups, more patients stopped using corticosteroids and NSAIDs than started, with overall decreases of 8.9% [95%CI 8.4-9.4%] for corticosteroids and 12.9% [95%CI 12.3-13.4%] for NSAIDs. The proportion of narcotic users changed little (overall decrease of 2.5% [95%CI 1.9-3.0%]).

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Conclusions—Use of all three co-therapies increased in the 6 months before initiation of new DMARD regimens for RA. Use of corticosteroids and NSAIDs decreased modestly 6-12 months fter initiation, but there was only a very small decrease in narcotic use. These differential changes require further study.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that can cause permanent joint damage and disability (1). Pain is common and caused by the inflammatory process and secondary osteoarthrosis (2). The goals of RA management are to prevent joint damage, loss of function, and to control pain. Early initiation of disease-modifying anti-rheumatic drugs (DMARDs) is aimed at controlling disease activity and preventing disease progression (3;4). Effective treatment for RA might not only control disease activity but also reduce the need for co-therapies such as corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotics that are mainly used to control symptoms.

Oral corticosteroids improve symptoms and may also reduce progression of RA (3;5). However, another goal of therapy is to minimize long term use of corticosteroids (6) because of their many side effects including osteoporosis, fractures, hypertension, weight gain, peptic ulcer disease, osteonecrosis, risk of infection, and increased cardiovascular risk (7-9). In addition to corticosteroids, two other main groups of drugs are used in RA for symptom control: NSAIDs and narcotics (10-12). NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors, increase the risk of peptic ulcers and gastrointestinal bleeding and also have adverse cardiovascular effects (13-15). Narcotic use, which is common among patients with RA (11;16-19), carries the risks of drug abuse, addiction, withdrawal syndrome, respiratory depression, and fractures (20;21). Reducing exposure to these co-therapies is desirable because it would decrease the incidence of therapy-related adverse outcomes in RA patients.

Although the efficacy of DMARDs in the treatment of RA is widely recognized (3), only a few small studies have addressed their effects on the use of corticosteroids and NSAIDs (12;22-24). These studies were restricted to biologic drugs and showed that the use of both, corticosteroids and NSAIDs, decreased 3 to 6 months after a biologic was started (22;23). For narcotics, one study addressed temporal trends in narcotic use among DMARD users (12), but the effect of DMARD initiation on narcotic use is not known. If DMARDs do improve pain and inflammation and allow reduction of these co-therapies, they could have ancillary benefits to patients beyond those documented in short-term clinical trials (25-28). Clinical trials generally do not allow for changes in these co-therapies during the controlled phase of the study (26;28) but observational studies allow these changes in therapy to be examined.

Effective DMARD treatments could reduce use of drugs used to treat RA symptoms. We hypothesized that the initiation of DMARD therapy would reduce the use of corticosteroids, NSAIDs and narcotics. To study the association between DMARD initiation and co-therapy use, we examined data from 4 major US administrative databases (frequently used for assessments of medication effects), that would allow broad extrapolation of our findings and also reflect clinical practice.

Materials and methods

This cohort study primarily assessed within-person differences in any use of oral corticosteroids, NSAIDs and narcotics (≥1 prescription) in the 6 months before, compared to the 6-12 months after initiating one of the study DMARD regimens.

Data source and study population

We assembled 4 retrospective cohorts of patients aged 18 years or older with a diagnosis of RA (ICD9-CM 714.*, except for 714.3) from 1998 to 2005 enrolled in Tennessee's Medicaid program (TennCare), Kaiser Permanente Northern California (KPNC), Pennsylvania Pharmaceutical Assistance Contract for Elderly (PACE), and individuals from 49 US states who were dually eligible for Medicaid and Medicare or for Medicaid alone (2000-2005) (MAX/MED). We excluded Tennessee enrollees from the MAX/MED cohort to avoid duplication. Patients entered the RA cohort on the date the first prescription for a specific DMARD regimen was filled (initiation date), if they met the following criteria: continuous enrollment for at least 1 year before entering the cohort (≤30 days gaps were allowed) and no prescription for that DMARD during this time period. We also excluded records with missing gender information and those of patients with other diseases that might warrant DMARD treatment including: psoriasis or psoriatic arthritis (ICD9-CM: 696.0, 696.1, 696.2), juvenile rheumatoid arthritis (ICD9-CM: 714.3), systemic lupus erythematosus (ICD9-CM: 710.0), Crohn's disease (ICD9-CM: 555), ulcerative colitis (ICD9-CM: 556), and ankylosing spondylitis (ICD9-CM: 720). Patients who lacked 1 year follow-up after the initiation date were also excluded from the analysis.

Exposure groups

The most common DMARDs used in RA are methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide (LEF), etanercept, infliximab and adalimumab (3;29;30). Five exposure groups were defined to examine whether initiation of common DMARD regimens is associated with change in use of co-therapies. The selection of these groups was based on common patterns of use observed in the cohorts. We excluded any patient who filled a biologic DMARD different from an anti-TNF drug (e.g. anakinra, abatacept, rituximab).

Exposure groups (Table 1) were defined as patients who filled a first prescription for a specific DMARD drug, with no prescription filled for the same DMARD during the year before the initiation date.

1. First MTX: patients who filled a first prescription for MTX and did not have any previous DMARD prescription filled in the year before the initiation date and did not have leflunomide or a biologic DMARD filled on the same day.
2. New MTX: patients who filled a first prescription for MTX and had a previous non-biologic DMARD filled but had no prescription for any biologic DMARD in the year before the initiation date.
3. New HCQ/SSZ: MTX failures (patients who filled a MTX prescription within the past 90 days) who filled a first prescription for either HCQ and/or SSZ and had no prescription filled for any biologic DMARD in the year before the initiation date.
4. New LEF: MTX failures (patients who filled a MTX prescription within the past 90 days) who filled a first prescription for LEF and had no prescription filled for any biologic DMARD in the year before the initiation date.
5. New anti-TNF: patients who filled a prescription for infliximab, etanercept or adalimumab with no anti-TNF use in the year before the initiation date. Previous and concurrent use of MTX or other DMARD was allowed, but filling two TNF-α antagonist on the same date was not. This group mainly includes patients who previously failed other non-biologic DMARDs. Any patient who filled a prescription for a anti-TNF drug different from infliximab, etanercept or adalimumab was excluded from the study (e.g. golimumab, certolizumab pegol)

Outcomes

The primary outcome was the overall change in the proportion (%) of users of oral corticosteroids, narcotics and NSAIDs in the 6-month period before DMARD initiation (P_0) compared to the 6-12 month period after initiation (P_{+12}) for each DMARD group in the 4 cohorts (Figure 2). We measured the use of these co-therapies in the 6-12 months (P_{+12}) after the new regimen was started to allow time for disease control to be achieved and titration or withdrawal of other medications. To better define patterns of change in co-therapies, we also explored the −12 to −6 month period before initiation (P_{-6}) and the period from initiation to 6 months later (P_{+6}) (Figure 1). Co-therapies use during each period was measured as follows:

1. Oral corticosteroids use measurements included the average daily dose for each 6 month period calculated as prednisone equivalents per day (mg/d), and the percentage of days with corticosteroid therapy (i.e. days of supply in each period/ 180 days*100).
2. NSAID use was measured as the percentage of days with NSAID therapy.
3. Narcotics use was measured as the percentage of days with narcotic therapy. We defined narcotics as natural, semi-synthetic and synthetic opioids (and combinations) that required a prescription, but we did not include opioids that are used to modulate gastrointestinal motility (e.g. laudanum, loperamide, diphenoxylate, difenoxin, etc).

These summary measurements included only patients that were taking the specific co-therapy at each time period, excluding non-users from the calculations.

Patient Characteristics

Other variables measured to describe users of DMARDs were: age, race, rural residence (yes/no), and co-morbidity (modified Charlson score).

Statistical Analysis

Corticosteroids, NSAIDs and narcotics users for each time period were described as percentages with 95% confidence interval (percent [95%CI]), while daily dose of corticosteroids and % days with a specific co-therapy were described as median values. Other continuous variables were represented as medians and interquartile ranges (median (IQR)) unless otherwise specified. We calculated the changes in the percentage of co-therapies users from P_0 to P_{+12} taking into account the correlation due to the paired measurements per subject. McNemar's tests were used to assess within-person differences in any use of oral corticosteroids, NSAIDs and narcotics (≥ 1 prescription) during 6 months before initiation (P_0) versus 6-12 months after initiation (P_{+12}) for the five DMARD regimens (Figure 2). Statistical analyses were performed using SAS version 9.2 (SAS Institute) and Stata version 11.0 (StataCorp). The study protocol was reviewed by the Tennessee's Bureau of TennCare and approved by Vanderbilt's Institutional Review Board (IRB), by University of Alabama at Birmingham IRB, by Partners Healthcare IRB, and by Kaiser Foundation Research Institution.

Results

Patient characteristics

We identified 32,476 RA patients who started a new DMARD regimen and had a full year of baseline and follow-up data available: 13% from TennCare, 18% from KPNC, 7% from PACE and 62% from MAX/MED. Study patients were mostly female, white and between

50-64 years old, except for PACE cohort enrollees that were all ≥65 years. Most were urban residents, except for the TennCare cohort where 53% lived in a rural area. Enrollment between 1998 and 2001 was consistent for most of the cohorts. The median Charlson score was 2 (IQR 1, 3) for PACE enrollees and 1 (IQR, 1, 2) for the other cohorts (Table 2).

DMARD (biologic and non-biologic) and co-therapy use

The distribution of patients that initiated different DMARD regimens differed among cohorts (Table 3). Between 25% and 30% of patients initiated an anti-TNF agent. In all the cohorts, etanercept was the most frequent biologic started, and accounted for 15% to 19% of all DMARD regimens initiated. The day before the initiation date, the point prevalence of patients using corticosteroids across the 4 cohorts ranged from 24% to 32%, NSAIDs from 32% to 39%, and narcotics from 15% to 33% (Table 3). KPNC (15.3%) and PACE (16.4%) had lower narcotic use than the other cohorts; the low narcotic use in PACE compared to TennCare and MAX/MED was not explained by age differences in these cohorts (data not shown).

The median dose of corticosteroids (mg/d of prednisone equivalents), the median percentage days of therapy, and the percentage of users for each co-therapy differed across cohorts for each period of time (Appendix 1).

Changes in corticosteroid use by DMARD groups

The overall percentage of patients with any use of corticosteroids increased from 43.7% [95%CI 43.2-44.2%] during P_{-6} (12 to 6 months before initiation) to 58.6% [95%CI 58.0-59.1%] during P_0 (the 6-month period prior initiation), and then decreased to 49.7% [95% 49.1-50.2%] during P_{+12} (6-12 months after initiation) (Figure 1A) (Appendix 1).

From P_0 to P_{+12}, approximately 10% to 20% of patients stopped corticosteroids while 5% to 12% started (Figure 2A), with an overall reduction of 8.9% [95%CI 8.4-9.4] in the prevalence of any corticosteroid use. Within each cohort, for most of the DMARD groups, the pair-wise analyses showed that more patients stopped corticosteroid than started ($p<0.005$ for all significant changes). In PACE, the pair-wise comparisons were not significant for new HCQ/SSZ (P=0.103), new LEF (P=0.327) and new anti-TNF (P=0.064) likely due to the small number of patients in this cohort (Figure 2A).

During P_0, the median dose of corticosteroid among corticosteroids users ranged from 2.3 to 9.5 mg/d of prednisone equivalents and the median percentage days with corticosteroid therapy ranged from 13% to 63% in the different DMARD groups for the 4 cohorts. During P_{+12}, the median dose of corticosteroid remained stable (ranged from 3.3 to 8.2 mg/d of prednisone equivalents) and the median percentage of days with corticosteroid therapy ranged from 42% to 62% in the different DMARD groups for the 4 cohorts (Appendix 1).

Changes in NSAID use by DMARD groups

During P_{-6}, the overall percentage of any use of NSAIDs was 64.1% [95%CI 63.5-64.6%], and increased to 69.1% [95%CI 68.6-69.6%] during P_0, but decreased to 56.2% [95%CI 55.6-56.7%] during P_{+12} (Figure 1B) (Appendix 1).

Comparing P_0 to $P_{+12,}$ between 13% and 30% of patients stopped NSAIDs and 5% to 15% started in the different DMARD groups in the 4 cohorts (Figure 2B), with an overall reduction in NSAID use of 12.9% [95%CI 12.3-13.4%] (Figure 1B). For most of the DMARD groups, the pair-wise analyses showed that more patients stopped NSAIDs than started ($p<0.005$ for all significant changes). In PACE, the pair-wise comparisons were not significant for new HCQ/SSZ (p=0.590) and new LEF (p=0.650) groups (Figure 2B).

The median percentage days with NSAID therapy among NSAID users ranged from 29% to 68% during P_0, and from 47% to 69% during P_{+12} in the different DMARD groups for the 4 cohorts (Appendix 1).

Changes in narcotic use by DMARD groups

The percentage of patients with any use of narcotics during P_{-6} was 58.7% [95%CI 58.2-59.2%], increased to 64.8% [95%CI 64.3-65.4%] during P_0, and then decreased to 62.7% [95%CI 62.1-63.2%] during P_{+12} (Figure 1C) (Appendix 1).

Comparing P_0 to P_{+12}, between 7% and 20% of patients stopped narcotics and 7% to 18% started narcotics in the 4 cohorts (Figure 2C); thus, a very small overall decrease (2.5% [95%CI 1.9-3.0%]) in the proportion of patients using narcotics was observed. The pair-wise analyses showed consistently that more patients stopped narcotics than started in the first MTX group in the 4 cohorts (all $p<0.05$ for all significant changes) (Figure 2C). Narcotic use also decreased among new MTX initiators from KPNC ($p<0.0001$), new HCQ/SSZ from TennCare ($p=0.015$), and new anti-TNF from MAX/MED ($p=0.01$) (Figure 2C).

The median percentage days with narcotic therapy among narcotic users in the 4 cohorts ranged from 10% to 49% during P_0, and from 16% to 62% during P_{+12} in the different DMARD groups for the 4 cohorts (Appendix 1).

Discussion

During RA treatment, corticosteroids, NSAIDs and narcotics are often prescribed to relieve symptoms until a DMARD exerts its therapeutic effect. Once this is achieved there should be less need for the use of these co-therapies and discontinuation should follow in some patients. We evaluated changes in the use of these co-therapies after initiation of different DMARD regimens.

Our major findings are that in patients with RA: 1) The use of medications to control symptoms increased in the 6 months immediately before a new DMARD regimen was initiated compared to the previous 6-12 month period, most likely representing worsening of the disease that led to the new DMARD regimen; 2) After a new DMARD regimen was started, more patients stopped use of corticosteroids and NSAIDs than started, which resulted in a 8.9% [95%CI 8.4-9.4%] decrease in the overall use of corticosteroids and 12.9% [95%CI 12.3-13.4%] for NSAID; 3) Narcotics were a common co-therapy in RA, but unlike corticosteroids and NSAID, there was only a very small decrease in their overall use after DMARD initiation.

The point prevalence of narcotic use at the initiation date was lower in KPNC (15.3%) and PACE (16.4%) compared to TennCare (32.5%) and MAX/MED (29.8%) This difference may reflect differences in clinical practice patterns or patient populations. Patients from TennCare and MAX/MED are Medicaid insured, whereas patients from KPNC receive integrated care with insurance through their employer, through self-insurance, or through Medicare or MediCal. Differences in socioeconomic status might also affect the availability of resources, the type of patients enrolled in each cohort, differences in patterns of care or use of specific medications. TennCare and MAX/MED include many patients with disabilities who may have more severe or chronic disease requiring narcotics to control pain. The reasons for lower narcotic use in PACE (which insures Medicare elderly patients) compared to TennCare and MAX/MED should be further investigated since the relative low use was not related to age or to the presence of other comorbidities.

DMARD initiation is associated with a reduction in corticosteroid use

Although the overall proportion of corticosteroid users did not decrease considerably, we found that more patients stopped corticosteroids than started, with an overall decrease of 9% in corticosteroid use. We also found that average dose of corticosteroids among users decreased slightly. This apparent corticosteroid-sparing effect is consistent with previous reports from small clinical studies (22-24;31) where anti-TNF therapy was associated with a reduction in corticosteroid use as early as 3 months after starting therapy and persisting after 5 years (22;32). The absolute decrease in the proportion of corticosteroid users, and the decrease in the median dose of corticosteroids among users after DMARD initiation, although both small, raised the possibility that improvement in disease control led to a decreased need for corticosteroids. Naumman et al. reported that corticosteroid use correlated with measures of disease activity during anti-TNF therapy, and that reduction in corticosteroid use occurred as disease activity improved (22). However, because we did not measure disease activity before and after treatment, it is important to consider other reasons for the decrease in corticosteroid use besides improvement of disease control, e.g. physician and patient desire to limit adverse effects associated with long-term use of corticosteroids.

The proportion of corticosteroid users among PACE patients in the new HCQ/SSZ, new LEF and new anti-TNF groups did not decrease significantly. Possible explanations are a small sample size in these exposure groups. It is important to point out that in our study, the HCQ/SSZ cohort is not a homogeneous group (see Table 1) and might contain patients with different disease activity. Consequently the observed increase in corticosteroid use in this cohort during P_{-6} compared to P_0 could represent disease worsening (for those patients who added HCQ/SSZ to previous MTX), disease improvement (patients who switched from MTX to HCQ), or medication toxicity (patients who switched from MTX to HCQ/SSZ).

DMARD initiation is associated with a reduction in NSAID use—Along with the decreased corticosteroid use, we found a similar pattern for NSAID use. The overall proportion of NSAID users decreased modestly (13%) after a new DMARD was started and the median percentage of days with NSAID therapy among the users remained unchanged, but for most of the groups there were more patients that stopped NSAIDs than started.

Pain control is one of the main goals in RA management, and although NSAIDs not only control pain but also reduce inflammation, few studies have examined the effects of DMARD initiation on NSAID use. Naumman et al. reported that the proportion of NSAID users decreased by16% (from 75% to 59%) after a year of anti-TNF therapy (22) among anti-TNF adherent patients. We found an overall reduction of NSAIDs use of almost 13% after the same period of time. The reasons for the lack of significance found in the new HCQ/SSZ and new LEF group for the PACE cohort might be the same as for corticosteroid use.

DMARD initiation is associated with a very small reduction in narcotic use

We found that the percentage of patients with any narcotic use decreased after a new DMARD was started, but the median percentage of days with narcotic therapy increased. If RA-associated pain was the reason for narcotic use, we would have expected use to decrease, as was observed with NSAIDs and corticosteroids. However, in patients that had failed a previous DMARD regimen the percentage of patients with any narcotic use remained unchanged. Clinical experience and previous reports showed that patients who failed MTX have more structural damage than patients who respond to therapy (33); pain from advanced structural damage might be more difficult to control potentially explaining the lack of a reduction in narcotic use.

Another explanation might be that after a DMARD regimen controls disease activity, physicians prefer to first taper medications with higher risk of serious side effects (gastrointestinal bleeding with NSAIDs, osteoporosis with corticosteroids, etc). Doses of narcotics used for pain control are considered relatively safe; therefore, tapering narcotics might be delayed (34;35). Studies with longer follow-up will be needed to clarify this hypothesis. Also, prolonged use of narcotics can cause dependence and make discontinuation difficult (36;37).

DMARD naïve patients who initiated MTX are more likely to decrease co-therapies use

Patients with recent onset RA with active disease are more likely to start with MTX (alone or in combination) as their first DMARD (3). Thus in our study, the first MTX group is likely to represent many patients with recently diagnosed RA. Notably, in this group, there was a decrease in co-therapy use with corticosteroids, NSAIDs, and also with narcotics. These results are consistent with a previous report in clinical practice, where first DMARD users experienced a greater reduction in levels of acute-phase reactants than those patients with previous DMARD courses (38). Patients in this group might have less joint and bone damage (33) and because their pain is related to inflammation, rather than structural damage (2) it might be more likely to be controlled by a DMARD.

Limitations

The results of our descriptive study must be interpreted in light of some caveats. First, we ascertained medication use using pharmacy fill data but actual adherence to therapies could not be measured. Nevertheless, pharmacy data are not subject to recall bias and have high concordance with patient's reports of medication (39;40). Second, although the remarkable consistency in findings across diverse patient populations suggests that decreased corticosteroid and NSAID use may be due to improved disease control due to DMARD initiation; other reasons for decreased use cannot be excluded. For instance, information on alternate indications for co-therapies were not available (e.g., narcotics might be prescribed for other reason such us chronic low back pain in some patients with RA). Third, use of over the counter NSAIDs was not measured, thus we cannot conclude that in some patients the initiation of a new DMARD regimen reduced all NSAIDs use. Fourth, the strength and dose of narcotics were not analyzed, therefore it is possible that some patients experienced disease improvement and reduced narcotic use (dose reduction or switch to less potent narcotic) without completely stopping narcotics. Finally, although we used one year of baseline information to define first MTX use, we cannot be certain that these patients were truly MTX naïve patients.

In summary, we found that the overall proportion of patients with RA prescribed corticosteroids and NSAIDs decreased by 9% and 13% respectively 6 to12 months after starting a new DMARD regimen. However, there was only a very small decrease in the proportion of patients using narcotics (2.5%) after initiation of new DMARD regimens. New studies using large data registries or clinical practices that include information on disease severity, pain levels, co-therapy indications, use of non-prescribed NSAIDs and adherence (including reason for non-adherence) would complement these data and help identify determinants of continued co-therapy use. Our study highlights the frequent use of co-therapies in RA patients despite use of specific RA treatments. Better and perhaps earlier treatment may help reduce use of these co-therapies and the adverse events associated with them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Significance and Innovation

- Use of co-therapies increased in the 6 months before initiation of new DMARD regimens for RA.

- In the 6-12 months after new DMARD initiation, the use of corticosteroids and NSAIDs decreased modestly but there was only a small decreased in narcotic use.

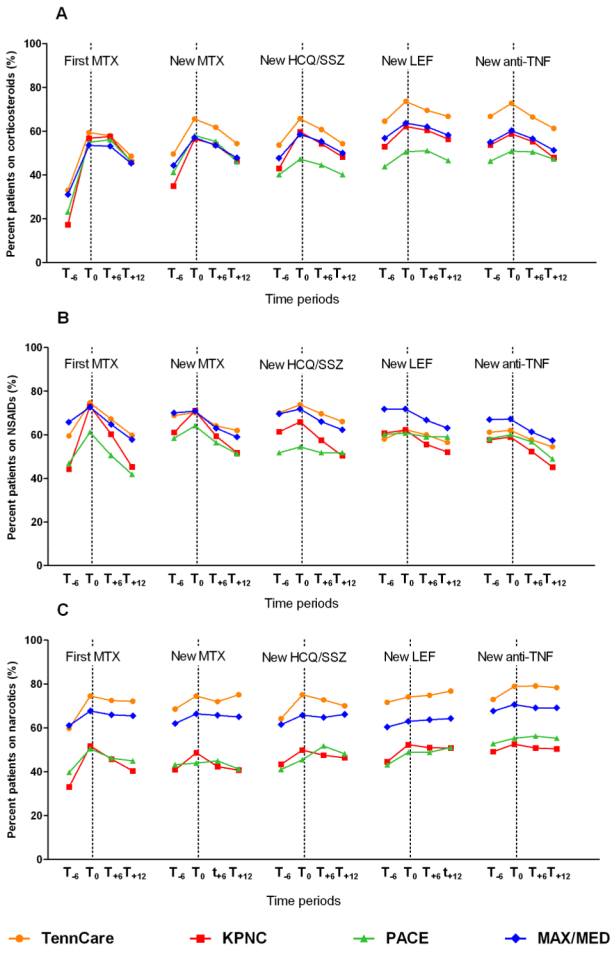

Figure 1.

Percent of patients with rheumatoid arthritis initiating a DMARD (disease modifying anti-rheumatic drug) regimen that used (any use) corticosteroids (**A**), NSAIDs (**B**) and narcotics (**C**). $\mathbf{P_{-6}}$ represents the 12 to 6 months period before DMARD initiation, $\mathbf{P_0}$ represents the 6 months period before DMARD initiation, $\mathbf{P_{+6}}$ represents the 6 months period after DMARD initiation, and $\mathbf{P_{+12}}$ represents the 6 to 12 months period after DMARD initiation. **MTX**: methotrexate; **HCQ**: hydroxychloroquine; **SSZ**: sulfasalazine; **LEF**: leflunomide; **TNF**: Tumor necrosis factor; **NSAIDs**: nonsteroidal anti-inflammatory drugs. **TennCare**: Tennessee's Medicaid program; **KPNC**: Kaiser Permanente Northern California program; **PACE**: Pennsylvania Pharmaceutical Assistance Contract for Elderly program; **MAX/MED**: Medicaid and/or Medicare program from 49 US states.

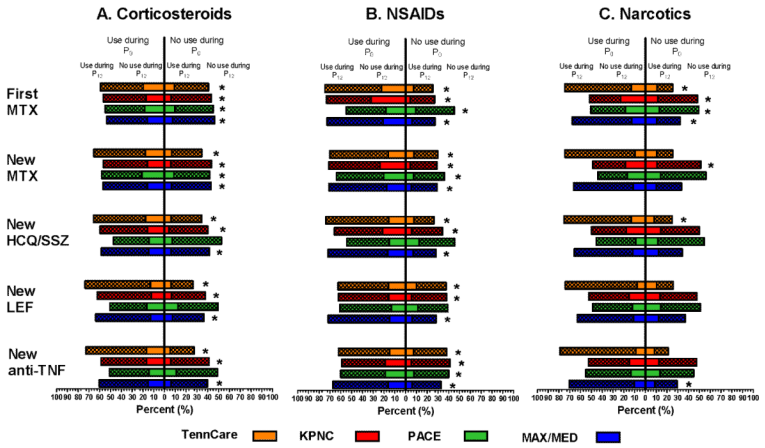

Figure 2.

Percentage of patients with rheumatoid arthritis that were using corticosteroids (**A**), NSAIDs (**B**) or narcotics (**C**) during $\mathbf{P_0}$ (6 months before DMARD initiation) and during $\mathbf{P_{+12}}$ (6 to 12 months after DMARD initiation). Solid pattern represents patients that switch user status (from non-users to users or vice versa) during $\mathbf{P_{+12}}$, and hatched pattern represents those patients that remained unchanged in their use of co-therapies during $\mathbf{P_{+12}}$. **(*)** indicates pair-wise analysis with p- values <0.05. **MTX**: methotrexate; **HCQ**: hydroxychloroquine; **SSZ**: sulfasalazine; **LEF**: leflunomide; **TNF**: Tumor necrosis factor; **NSAIDs**: nonsteroidal anti-inflammatory drugs. **TennCare**: Tennessee's Medicaid program; **KPNC**: Kaiser Permanente Northern California program; **PACE**: Pennsylvania Pharmaceutical Assistance Contract for Elderly program; **MAX/MED**: Medicaid and/or Medicare program from 49 US states.

Table 1

Description of disease modifying anti-rheumatic drug (DMARD) groups

DMARD Groups	Definitions
First MTX	New user of MTX: • No DMARD → MTX
New MTX	Switch from any other non-biologic DMARD to MTX • HCQ → MTX • SSZ → MTX • Other synthetic DMARD → MTX
New HCQ/SSZ	Switch or add HCQ and/or SSZ in a current MTX user • MTX → HCQ • MTX → SSZ • MTX → HCQ + MTX • MTX → SSZ + MTX • MTX → HCQ+ SSZ + MTX
New LEF	Switch or add LEF in a current MTX user • MTX → LEF • MTX → LEF + MTX • Other(s) synthetic DMARD + MTX → LEF • Other(s) synthetic DMARD + MTX → LEF + MTX • Other(s) synthetic DMARD + MTX → LEF + synthetic DMARD
New anti-TNF	First prescription of infliximab, etanercept, adalimumab with or without another non-biologic DMARD • Synthetic DMARD → TNF-α antagonist • Synthetic DMARD → TNF-α antagonist + synthetic DMARD

MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulfasalazine, LEF: leflunomide, TNF: Tumor necrosis factor

Table 2

Baseline Characteristics of RA patients initiating new episodes of DMARDs use (1998-2005)

Characteristics	COHORTS			
	TennCare (n=4383)	**KPNC (n=5695)**	**PACE (2133)**	**MAX/MED (n=20265)**
Age				
• Less than 50 years	1461 (33.3%)	1636 (28.7%)	--	6060 (29.9%)
• 50 to 64 years	1966 (44.9%)	2281 (40.1%)	--	7456 (36.8%)
• 65 years or older	956 (21.8%)	1778 (31.2%)	2133 (100%)	6749 (33.3%)
Female	3383 (77.2%)	4396 (77.2%)	1926 (90.3%)	17688 (87.3%)
Race				
• Caucasian	3242 (74.0%)	3737 (65.6%)	1911 (89.6%)	11889 (58.7%)
• African-American	607 (13.9%)	521 (9.2%)	178 (8.4%)	3829 (18.9%)
• Other/Unknown	534 (12.2%)	1437 (25.2%)	44 (2.1%)	4547 (22.4%)
Rural residence	2334 (53.3%)	115 (2.0%)	232 (10.9%)	5847 (28.9%)
Enrollment year				
• 1998	416 (9.5%)	523 (9.2%)	307 (14.4%)	---
• 1999	645 (14.7%)	805 (14.1%)	377 (17.7%)	---
• 2000	565 (12.9%)	799 (14.0%)	312 (14.6%)	2 (0.0%)
• 2001	527 (12.0%)	764 (13.4%)	232 (10.9%)	4161 (20.5%)
• 2002	608 (13.9%)	728 (12.8%)	284 (13.3%)	3668 (18.1%)
• 2003	796 (18.2%)	1024 (18.0%)	309 (14.5%)	6181 (30.5%)
• 2004	818 (18.7%)	1036 (18.2%)	300 (14.1%)	6192 (30.6%)
• 2005	8 (0.2%)	16 (0.3%)	12 (0.6%)	61 (0.3%)
Charlson score Median (IQR)	1 (1-2)	1 (1-1)	2 (1-3)	1 (1-2)

RA: Rheumatoid arthritis; DMARD: disease modifying anti-rheumatic drug; Charlson score is shown as median (interquartile range). **TennCare**: Tennessee's Medicaid program; **KPNC**: Kaiser Permanente Northern California program; **PACE**: Pennsylvania Pharmaceutical Assistance Contract for Elderly; **MAX/MED**: Medicaid and/or Medicare program from 49 US states.

Table 3

Patterns of new DMARD use and co-therapies in RA patients (1998-2005)

Characteristics	COHORTS			
	TennCare (n=4383)	**KPNC (n=5695)**	**PACE (2133)**	**MAX/MED (n=20265)**
DMARDs				
1. First MTX	1668 (38.1%)	1359 (23.9%)	885 (41.5%)	6741 (33.3%)
2. New MTX	660 (15.1%)	1443 (25.3%)	298 (14.0%)	3686 (18.2%)
3. New HCQ/SSZ	492 (11.2%)	689 (12.1%)	112 (5.3%)	1698 (8.4%)
4. New LEF	407 (9.3%)	745 (13.1%)	176 (8.3%)	1835 (9.1%)
5. New anti-TNF	1156 (26.4%)	1459 (25.6%)	662 (31.0%)	6305 (31.1%)
Co-therapies use the day before DMARD initiation				
• Corticosteroids	1373 (31.1%)	1822 (32.0%)	521 (24.4%)	5789 (28.6%)
• NSAIDs	1670 (38.1%)	2010 (35.3%)	675 (31.7%)	7852 (38.8%)
• Narcotics	1424 (32.5%)	872 (15.3%)	349 (16.4%)	6048 (29.8%)

DMARD: disease modifying anti-rheumatic drug; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; TNF: Tumor necrosis factor; NSAIDs: nonsteroidal anti-inflammatory drugs **TennCare**: Tennessee's Medicaid program; **KPNC**: Kaiser Permanente Northern California program; **PACE**: Pennsylvania Pharmaceutical Assistance Contract for Elderly program; **MAX/MED**: Medicaid and/or Medicare program from 49 US states.