Hindawi
Journal of Clinical Pharmacy and Therapeutics
Volume 2024, Article ID 8040681, 7 pages
https://doi.org/10.1155/2024/8040681

Research Article

Use of Analgesic and Anti-Inflammatory Medicines before and after Initiation of Biological Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis

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Received 30 October 2023; Revised 16 December 2023; Accepted 16 February 2024; Published 23 February 2024

Academic Editor: Md Saquib Hasnain

Background. Rheumatoid arthritis (RA) is an inflammatory condition that causes joint damage and is associated with pain. The biological disease-modifying antirheumatic drugs (bDMARDs) for RA are linked to additional therapeutic benefits as they suppress the inflammatory process, which in turn prevents joint erosion and reduces pain. Thus, the use of bDMARDs has the potential to reduce the need for other analgesic and anti-inflammatory therapies for RA. The aim of this study was to examine the analgesic and anti-inflammatory use around the initiation of bDMARDs. *Methods*. A cohort study was conducted using a 10% random sample of the population dispensing medicines under the Australian Pharmaceutical Benefits Scheme. People who initiated the first bDMARD for RA between 2014 and 2018 were included. The proportion who received any analgesic or anti-inflammatory, including nonsteroidal anti-inflammatory drugs, opioids, or glucocorticoids, in the twelve months prior to and post-bDMARD initiation was determined and compared using regression models. *Results*. There were 18,360 persons in the cohort, with a mean age of 55 years, and 69% were women. The use of any analgesic or anti-inflammatory in both tumor necrosis factor inhibitor (TNFi) and non-TNF initiators increased prior to initiation of bDMARD–from 43% to 52% in TNFi and from 52% to 63% in non-TNF initiators. In both groups, overall use decreased significantly post initiation to 37% and 42% in TNFi and non-TNF initiators, respectively ($p < 0.0001$). bDMARD initiation was associated with lower use of glucocorticoid therapy, but there was no decreasing effect on opioid use. *Conclusion*. While the use of any analgesic or anti-inflammatories decreased post-initiation of bDMARDs for RA, more than one-third of people were dispensed analgesic or anti-inflammatory agents twelve months post initiation. Ongoing review of the need for analgesic and glucocorticoids appears warranted, with assessment of nonpharmacological approaches to support pain management.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition that causes joint damage, pain, and disability [1]. In 2017-2018, the prevalence of rheumatoid arthritis in Australia was 2% according to the Australian Bureau of Statistics National Health Survey [2]. The disorder affects more women than men (2.3% vs 1.5%), with onset usually between 35 and 60 years [2]. The condition had a hospitalisation rate of 43 per 100,000 persons in 2017-2018 [2].

Pain is a common complication of inflammation [3]. Pain can impair physical functioning, daily activities, and emotional wellbeing [4]. Historically, RA treatment targeted the control of symptoms and pain management. With the development of disease-modifying antirheumatic drugs (DMARDs), the treatment goal has shifted to achieving remission or low disease activity as these drugs interfere with the disease process and slow down clinical and radiographic progression [5]. Conventional DMARD monotherapy is recommended as a first-line treatment, while biological DMARDs, including tumor necrosis factor inhibitor (TNFi)

and non-TNFi, are recommended when there is insufficient response to conventional DMARDs [6–8]. Biologic DMARDs have been shown to provide additional therapeutic benefits as they suppress the inflammatory process, which in turn prevents joint erosion and reduces pain [9].

Effective treatment might not only control the RA activity but also reduce the need of co-therapies for analgesia and inflammation, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and opioids [10].

Several studies have found that the use of glucocorticoids decreased after TNF biologic DMARD was started in patients with RA [10–14], and one study reported a decrease in glucocorticoid use after non-TNF in people with RA [15]. Two studies investigated changes in opioid use in patients with RA and found little change in overall opioid use after TNFi initiation [10, 16]. Kawai et al. [10] also looked at changes in NSAID use and found a decrease after TNFi initiation. However, there are no published data on patterns of analgesic and anti-inflammatory use (NSAIDs, opioids, and glucocorticoids) in patients with rheumatic conditions treated with biologic DMARDs in Australia.

1.1. Aim of the Study. This study aimed to determine the patterns of analgesic and anti-inflammatory use in people who initiated biological disease-modifying antirheumatic drugs (bDMARDs) therapy for rheumatic arthritis.

2. Materials and Methods

2.1. Study Population. Deidentified patient level data from a 10% random sample of the population from the Australian National Pharmaceutical Benefits Scheme (PBS) prescription database dispensed between 1 January 2013 and 31 December 2019 were utilised. Since mid-2012, PBS data represent the full capture of dispensing records for both general and concessional beneficiaries. A cohort study was undertaken on concessional and general patients to determine the extent of dispensing of analgesic and anti-inflammatory medicines (nonsteroidal anti-inflammatory drugs opioids and glucocorticoids) prior to and post initiation of biologic DMARD therapy for rheumatoid arthritis. Biologic DMARD therapy used for rheumatic arthritis includes therapy with tumor necrosis factor inhibitors (TNFi) and non-TNF agents. All patients who had their first ever (index) bDMARD dispensed with an indication for rheumatoid arthritis between 1 January 2014 and 31 December 2018 were identified as the bDMARD initiating cohort. Proportions of the cohort who were dispensed with nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, or glucocorticoids each month in the twelve months prior to and including the month of bDMARD therapy initiation, as well as in the twelve months post initiation were determined. In Australia, subsidised medicines are mostly dispensed equivalent to one month's supply. Thus, the rate of use of any or a given analgesic or anti-inflammatory class (NSAIDs, opioids, or glucocorticoids) each month prior to bDMARD initiation was defined as the proportion of the cohort who received at least one dispensing of that class in that month. In the month of bDMARD initiation and in the months post, at the level of the class (NSAIDs, opioids, or glucocorticoids), the use was defined as the proportion of the cohort who received at least one dispensing for that class in that month noting that the analgesic and anti-inflammatory could have been dispensed with or without bDMARD. People who died in the 12 months post-bDMARD initiation were excluded.

The results are presented by the type of bDMARD at initiation: TNF inhibitors and non-TNF agents and demographics (mean age and gender) at the time of initiation are included.

All results have been multiplied by a factor of 10 to obtain estimates for the overall population.

2.2. Statistical Analysis. To examine changes in analgesic and anti-inflammatory use over time, rate ratios (RRs) were estimated using Poisson regression models comparing the rate of use in one month to the previous month in (a) the twelve months prior to the month of bDMARD therapy initiation, and (b) in the twelve months post bDMARD initiation. The month of bDMARD initiation was excluded from the Poisson regression model to allow time for uptake and withdrawal. Proportions were compared using chi-square tests, while mean age was compared using Student's *t*-test. All analyses were undertaken for all analgesic and anti-inflammatory groups in each cohort. Analyses were performed using SAS 9.4 Statistical Package (SAS Institute, Cary NC, USA).

2.3. Medicines Included in the Analyses. Medicines were coded in accordance with the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system [17].

Biological disease-modifying antirheumatic drugs for rheumatic arthritis which were included in the analysis: tumor necrosis factor inhibitors (TNFi) are as follows: etanercept (L04AB01), infliximab (L04AB02), adalimumab (L04AB04), golimumab (L04AB06), and certolizumab pegol (L04AB05). Non-TNF biologics are as follows: rituximab (L01XC02), abatacept (L04AA24), anakinra (L04AC03), and tocilizumab (L04AC07). The medicines were identified by their restriction codes, with analyses limited to these products subsidised for rheumatoid arthritis.

NSAIDs included in the analysis are as follows: indometacin (M01AB01), sulindac (M01AB02), diclofenac (M01AB05), piroxicam (M01AC01), meloxicam (M01AC06), ibuprofen (M01AE01), naproxen (M01AE02), ketoprofen (M01AE03), tiaprofenic acid (M01AE11), mefenamic acid (M01AG01), celecoxib (M01AH01), rofecoxib (M01AH02), and limiracoxib (M01AH06). Systemic glucocorticoids included in the analysis are as follows: betamethasone (H02AB01), dexamethasone (H02AB02), methylprednisolone (H02AB04), prednisolone (H02AB06), prednisone (H02AB07), triamcinolone (H02AB08), hydrocortisone (H02AB09), and cortisone (H02AB10). Opioids included in the analysis are as follows: codeine (N02AA),

codeine in combination (N02AJ06, N02AA59), morphine (N02AA01), hydromorphone (N02AA03), oxycodone (N02AA05, N02AA55), pethidine (N02AB02), fentanyl (N02AB03), buprenorphine (N02AE01), tramadol (N02AX02), tapentadol (N02AX06), and methadone (N02AC02).

3. Results

There were 18,360 unique people who initiated bDMARD therapy for rheumatoid arthritis between 1 January 2014 and 31 December 2018. The mean age at initiation was 55 years (SD = 15.1), with 69% being women.

Among the 18,360 people, 88% initiated TNF inhibitors and 12% initiated non-TNF agents. The mean age and gender of the TNF and non-TNF cohorts at the time of initiation are presented in Table 1. People who initiated TNF inhibitors were significantly younger with a mean age of 54 years compared to people who initiated non-TNF agents (mean age 61). In both groups, more women than men initiated biologic DMARDs.

Proportions of people who used analgesic or anti-inflammatory agents pre- and postinitiation of TNFi and non-TNF agents for rheumatoid arthritis are summarised in Tables 2 and 3. Figures 1 and 2 present the patterns of use in a graphical form.

3.1. TNFi Initiators. Forty three percent of TNFi initiators were dispensed at least one analgesic or anti-inflammatory in month twelve prior to index TNFi, which decreased to 37% in month twelve post-TNf initiation (chi-square, $p < 0.0001$, Table 2). While the use of analgesics or anti-inflammatory increased significantly by 1.4% each month prior to TNFi initiation (up to 52% in the month immediately prior to index TNFi), it then decreased significantly by 1.4% each month post TNFi initiation (Table 3).

Glucocorticoids were increasingly used closer to TNFi initiation (from 21% in month twelve prior up to 33% in the month immediately but then significantly decreased to 17% in month twelve post initiation (Tables 2 and 3).

The use of opioids was increasing both prior to and post-index TNFi, but the increase was at a slower pace (non-significant) after initiation (Table 3). The overall change was from 15% in month twelve prior up to 17% in month twelve post index TNFi (chi-square, $p = 0.112$, Table 2).

NSAIDs use was decreasing significantly prior to and post TNFi initiation (Table 3). The overall change was from 19% in month twelve prior down to 13% in month twelve post index TNFi (chi-square, $p < 0.0001$, Table 2).

3.2. Non-TNF Initiators. Fifty two percent of non-TNF initiators were dispensed at least one analgesic or anti-inflammatory in month twelve prior to index non-TNF, which decreased post-initiation down to 42% in month twelve (chi-square, $p < 0.0001$, Table 2). While the use increased significantly by 1.0% each month prior to non-TNFi initiation (up to 63% in the month immediately prior to index non-TNFi), it then decreased significantly by 2.2% each month post non-TNFi initiation (Table 3).

Glucocorticoids were increasingly used prior to non-TNF initiation, but then their use significantly decreased (Table 3). The overall change was from 32% in month twelve prior down to 19% in month twelve post index non-TNF (chi-square, $p < 0.0001$, Table 2).

Opioids and NSAIDs use was relatively stable with a slight increase in use in the month immediately prior to non-TNF initiation. The use did not change after initiation of non-TNF (Tables 2 and 3). Around 20% of people received opioids and around 16% of people received NSAIDs and in any month prior and post index non-TNF.

4. Discussion

Our results show that bDMARD initiation was associated with lower use of glucocorticoid therapy, but the impact on analgesic use was less pronounced with no decreasing effect on opioid use. In the year prior to TNFi initiation, the use of analgesics or anti-inflammatory increased from 43% twelve months prior to initiation up to 52% in the month immediately prior to index TNFi. A similar trend was observed in non-TNF initiators. This increased use of pain medicine likely reflects the worsening of the disease which led to the initiation of bDMARD. Once bDMARD was initiated, the use of any analgesic or anti-inflammatory agent significantly decreased to 37% and 42% in month twelve post-TNFi and non-TNF initiators, respectively; however, this was largely driven by decreased use of systemic glucocorticoids.

Glucocorticoid use was found to decrease post-bDMARD initiation, down to 17% and 19% at month twelve post-TNFi and non-TNF initiation. This result is consistent with several other studies that also found that the use of glucocorticoids decreased after initiation of TNFi in patients with RA [10–14], and one study reported a decrease in glucocorticoid use after non-TNF in people with RA [15]. However, the results are still indicative of potential over-reliance on glucocorticoids. The 2021 ACR Guidelines recommend against the use of long-term (≥3 months) glucocorticoid therapy [18].

When stratified by class, NSAIDs use decreased significantly from 19% prior to TNFi initiation to 13% post initiation, which is consistent with a study by Kawai et al. [10] reporting a decrease in NSAIDs use after TNFi initiation. NSAIDs are mainly used to control pain and reduce inflammation in people with RA and once TNF therapy brings the disease under control the need of co-therapy with NSAID decreases [10].

Opioid use, however, was not affected by initiation of bDMARDs, increasing from 15% prior to TNFi initiation up to 17% post initiation. Several other studies also found little change in opioid use after TNFi initiation [10, 16]. These results suggest overreliance on opioids for analgesia. The

Table 1: Demographics characteristics at time of initiation of biologic disease-modifying antirheumatic drugs (bDMARD), by type.

Type of bDMARD	TNF inhibitors (N = 16,380)	Non-TNF agents (N = 1,980)	p value
Mean age, years (SD)	54 (SD = 15.2)	61 (SD = 12.4)	<0.0001[a]
Gender			
Females, n (%)	11,260 (69%)	1390 (70%)	0.185[b]
Males, n (%)	5,120 (31%)	590 (30%)	

[a]Student's t-test was used to compare mean age between two groups. [b]Chi-square test was used to compare proportions between two groups. TNF ⟶ tumor necrosis factor. Non-TNF ⟶ non-tumor necrosis factor.

Table 2: Analgesic or anti-inflammatory use pre and post biologic disease-modifying antirheumatic drugs (bDMARD) in people with rheumatoid arthritis.

Type of initiated bDMARD	Type of analgesics/anti-inflammatories	Month 12 pre index month (%)	Month 1 pre index month (%)	Month 1 post index month (%)	Month 12 post index month (%)	p value[a] (month 12 post to month 12 pre index)
TNFi	Any analgesic or anti-inflammatory	43	52	43	37	<0.0001
	Glucocorticoids	21	33	25	17	<0.0001
	Opioids	15	17	15	17	0.112
	NSAIDs	19	16	15	13	<0.0001
Non-TNF	Any analgesic or anti-inflammatory	52	63	58	42	<0.0001
	Glucocorticoids	32	39	34	19	<0.0001
	Opioids	20	25	22	20	0.694
	NSAIDs	16	20	18	16	0.664

Note. Index month is the month of bDAMRD initiation. [a]Chi-square test was used to compare proportions. TNFi ⟶ tumor necrosis factor inhibitor. Non-TNF ⟶ on-tumor necrosis factor. NSAIDs ⟶ nonsteroidal anti-inflammatory drugs.

Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis [19] conditionally recommends not using opioids routinely for the treatment of pain in RA, and that if opioids are required the use should only be brief.

The lack of decrease in opioid use suggests that non-pharmacological approaches need to be incorporated into pain management. While inflammation from the disease itself is a driver of pain, it is also increasingly recognised that there is a nociplastic contribution to pain in rheumatoid arthritis [20]. Pain, neuroscience education, mindfulness, cognitive behavioural therapy, and acceptance and commitment therapy have all been found to contribute to improvements in pain or function and could be trialed as strategies for improving pain and reducing opioid use in persons with rheumatoid arthritis [21–24].

We analyzed data from a national dataset capturing prescription data of 10% of all Australians who received medicines under PBS. We included both general and concessional beneficiaries as since 2012 all copayment prescriptions are recorded in the PBS data, allowing for generalization of the results to the entire Australian population. Furthermore, administrative pharmacy data are not subjective to recall bias.

There are few limitations of the study. While bDMARDS are listed according to their indication of use, there is a lack of information on the indication for use for the analgesics and anti-inflammatories analysed in this study. Thus, there is a possibility that the analgesic or anti-inflammatory was taken for conditions other than RA. For example, NSAIDs could be taken for other non-inflammatory conditions such as migraine, period pain and fever. We are not able to ascertain if the dispensed medicines were actually taken. Some NSAIDs are available over-the-counter in Australia, which means that our NSAID use might be underestimated. Our analysis was limited to the use of prescription medicine use only, we were not able to ascertain the extent of use of other pain relief services or activities, such as hydrotherapy and

Table 3: Changes in analgesic or anti-inflammatory use pre and post biologic disease-modifying antirheumatic drugs (bDMARD) in people with rheumatoid arthritis.

Type of initiated bDMARD	Medicine	Prior 12 months (index − 12 to index − 1)			Post 12 months (index + 1 to index + 12)		
		Average month-to-month change (%)	Rate ratio (95% CI)	p value[a]	Average month-to-month change (%)	Rate ratio (95% CI)	p value[a]
TNFi	Any analgesic or anti-inflammatory	+1.4%	1.014 (1.009; 1.019)	<0.0001	−1.4%	0.986 (0.981; 0.991)	<0.0001
	Glucocorticoids	+3.4%	1.034 (1.024; 1.043)	<0.0001	−3.2%	0.968 (0.959; 0.976)	<0.0001
	Opioids	+1.0%	1.010 (1.001; 1.020)	0.034	+0.4%	1.004 (0.998; 1.009)	0.166
	NSAIDs	−1.4%	0.986 (0.978; 0.994)	0.001	−1.0%	0.990 (0.985; 0.994)	<0.0001
Non-TNF	Any analgesic or anti-inflammatory	+1.0%	1.010 (1.003; 1.018)	0.009	−2.2%	0.978 (0.967; 0.990)	0.001
	Glucocorticoids	+1.7%	1.017 (1.004; 1.031)	0.009	−3.8%	0.962 (0.946; 0.978)	<0.0001
	Opioids	+0.4%	1.004 (0.989; 1.020)	0.582	−1.4%	0.986 (0.971; 1.001)	0.063
	NSAIDs	+0.7%	1.007 (0.987; 1.026)	0.492	−1.1%	0.989 (0.971; 1.007)	0.227

[a]p value for the ratio of the rate in one month to the rate in the previous month was calculated using a Poisson regression model accounting for over/under dispersion in the data and autoregression. *Note*. The index month of TNFi or non-TNFi initiation was excluded from the Poisson regression models to allow time for uptake/withdrawal. TNFi ⟶ tumor necrosis factor inhibitor. Non-TNF ⟶ non-tumor necrosis factor. NSAIDs ⟶ nonsteroidal anti-inflammatory drugs.

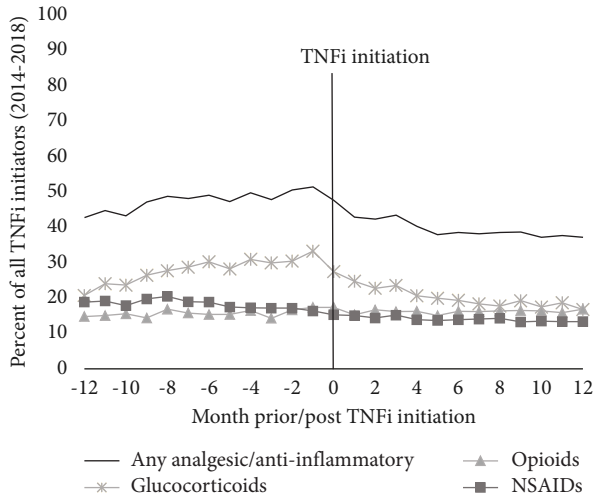

Figure 1: Use of analgesics or anti-inflammatories prior and post initiation of tumor necrosis factor inhibitors for rheumatoid arthritis.

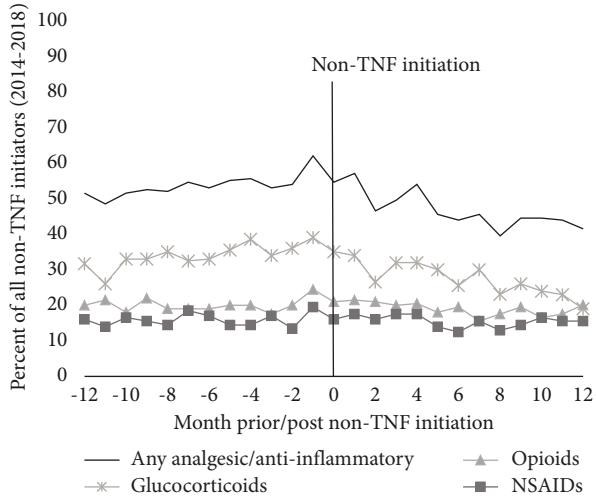

Figure 2: Use of analgesics or anti-inflammatories prior and post initiation of nontumor necrosis factor agents for rheumatoid arthritis.

exercise programs, psychologist, physiotherapy, or exercise physiology services. We were not able to adjust for disease severity.

5. Conclusions

The use of any analgesic or anti-inflammatory decreased after initiation of biologic DMARDs for rheumatoid arthritis. However, more than one-third of people were still dispensed analgesic or anti-inflammatory agents twelve months post initiation bDMARD initiation. Ongoing review of the need for analgesic and glucocorticoid use appears warranted, as does the opportunity for integration of nonpharmacological approaches to support pain management while minimising the potential for medicine harms.

Data Availability

PBS data are available under license at the request of the data custodian.

Ethical Approval

The study used deidentified data and conforms to the management and release of data in accordance with the principals of the Australian Government Privacy Act, 1988. The study was approved by the External Request Evaluation Committee (RMS1092).

Consent

The study uses personally nonidentifiable data, and thus, we did not obtain informed consent for participation.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was funded under the Australian Government Department of Health Value in Prescribing Initiative.

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