Comparison of glucocorticoids and painkiller prescribed days between rheumatoid arthritis patients receiving early and late treatment with a biological agent via a population-based cohort study.

Zon-Min Lee[1], Yao-Hsu Yang[2], Ho-Chang Kuo[1], Ya-Han Shen[1], Hong-Ren Yu[1], and Yu-Jih Su[1]

[1]Chang Gung Memorial Hospital Kaohsiung Branch
[2]Chang Gung University

September 28, 2020

Abstract

Comparison between early biologics treatment and late biologics treatment of rheumatoid arthritis (RA) patients in decreasing prescription days of glucocorticoids and painkillers by using the Taiwan National Health Insurance Research database from January 1, 1997 to December 31, 2013. We defined early use of biologics as biologics prescribed within 2.24 years after the RA diagnosis, and the late use of biologics was defined as those prescribed after 2.24 years of the RA diagnosis. These definitions are based on previous studies defining early arthritis as arthritis within 2 years of diagnosis, while we needed another 3 months for application biologics here in Taiwan, which equals a total of 2.24 years. Among the 821 patients, 410 patients (50%) were classified in the Early group, and the other 411 patients (50%) were classified in the Late group. The use of any of these three types of medication, including steroids, disease modifying antirhuematic drugs, and nonsteroid anti-inflammatory drug (NSAID) was changed significantly after biologics treatment. Comparing between before and after biologics treatment, oral medication was significantly tapered (all p <0.0001). The results show that men are 1.81 times more likely than women to taper oral glucocorticoids and NSAIDs. Younger age (<45) patients are 1.91 times more likely to taper steroids and NSAIDs than those aged over 65 years old. Both gender and age were found to be independent factors that could decrease days of prescription of both steroids and NSAIDs in early use of biologics agents. This study indicates that younger patients only need short-term (2.53±1.92 years, p=0.03) and early treatment with biologics (within 2.24 years of diagnosis of RA), just in order to taper steroids and NSAIDs to less than 50% than before biologics treatment.

Comparison of glucocorticoids and painkiller prescribed days between rheumatoid arthritis patients receiving early and late treatment with a biological agent via a population-based cohort study.

Zon-Min Lee, MS[1], Yao Hsu Yang, MD, PhD[2-4], Ho-Chang Kuo, MD, PhD[5], Ya-Han Shen[6], Hong-Ren Yu, MD,PhD[7*], Yu-Jih Su, MD, PhD[8*]

[1]Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Taiwan 83301

[2]Department of Traditional Chinese Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan

[3]Health Information and Epidemiology Laboratory of Chang Gung Memorial Hospital, Chiayi, Taiwan

[4]School of Traditional Chinese Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan

[5]Kawasaki Disease Center and Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Taiwan 83301

[6]Biostatistics Center, Kaohsiung Chang Gung Memorial Hospital, Taiwan 83301

[7]Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Taiwan 83301

[8]Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan 83301

Yu-Jih Su and Hong-Ren Yu contributed equally to this manuscript

Corresponding Author:

Yu-Jih Su

Tel: +886-7-7317123 ext 8800

Fax: +886-7-7322402

E-mail: *bensu8@gmail.com*

Acknowledgements

We appreciated the Biostatistics Center, Kaohsiung Chang Gung Memorial Hospital for statistics work. We also appreciated the Kawasaki Center and Mitochondria center, Kaohsiung Chang Gung Memorial Hospital for assistance.

Authors' contributions Zon-Min Lee: Drafting the article and revising it critically for important intellectual content Yao Hsu Yang: acquisition of data, analysis and interpretation of data Ho-Chang Kuo: analysis and interpretation of data Ya-Han Shen: acquisition of data and analysis Hong-Ren Yu: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved Yu-Jih Su: Substantial contributions to conception, design, discussion, and final approval of the version to be published

Declarations This study has been approved by Institutional Review Board (IRB) of Chang Gung Memorial Hospital: 201801196B0C501 Competing interests All authors hereby declare that they have no financial interests to disclose in relation to this article.

Funding This study was funded by the following grants: CFRPG8H0231 from Chang Gung Memorial Hospital in Taiwan.

Abstract

Aim: Comparison between early biologics treatment and late biologics treatment of rheumatoid arthritis (RA) patients in decreasing prescription days of glucocorticoids and painkillers by using the Taiwan National Health Insurance Research database from January 1, 1997 to December 31, 2013.

Method: We defined early use of biologics as biologics prescribed within 2.24 years after the RA diagnosis, and the late use of biologics was defined as those prescribed after 2.24 years of the RA diagnosis. These definitions are based on previous studies defining early arthritis as arthritis within 2 years of diagnosis, while we needed another 3 months for application biologics here in Taiwan, which equals a total of 2.24 years.

Results: Among the 821 patients, 410 patients (50%) were classified in the Early group, and the other 411 patients (50%) were classified in the Late group. The use of any of these three types of medication, including steroids, disease modifying antirhuematic drugs, and nonsteroid anti-inflammatory drug (NSAID)

was changed significantly after biologics treatment. Comparing between before and after biologics treatment, oral medication was significantly tapered (all p <0.0001). The results show that men are 1.81 times more likely than women to taper oral glucocorticoids and NSAIDs. Younger age (<45) patients are 1.91 times more likely to taper steroids and NSAIDs than those aged over 65 years old. Both gender and age were found to be independent factors that could decrease days of prescription of both steroids and NSAIDs in early use of biologics agents.

Conclusion: This study indicates that younger patients only need short-term (2.53±1.92 years, p=0.03) and early treatment with biologics (within 2.24 years of diagnosis of RA), just in order to taper steroids and NSAIDs to less than 50% compared to the steroids and NSAIDs doses before biologics treatment.

Keywords: rheumatoid arthritis, biological agent, cohort study, cumulative days, steroid, painkillers, NSAID

Key points:

1. Treatment with biologics within 2.24 years of rheumatoid arthritis lessen the days of prescription of glucocorticoids and painkillers in 12 months. (Table 2)
2. Take whole rheumatoid arthritis disease duration into consideration, using biologics treatment in the early quartile, i.e. using biologics longer than 75% of disease duration, significantly reduced the prescription days of steroid. (Table 3)
3. Gender and the age by the time of using biologics are two independent factors associated with decreasing at least half of the prescription days of glucocorticoids and other traditional treatments. (Table 4)
4. The reimbursement of biologics other than the Etanercept and the Adalimumab as first-line biologics treatment was not available in Rituximab and Tocilizumab by 2013, and the Golimumab was not available until the end of 2012, which could limit the case numbers in this research. (Limitation)

Introduction

Rheumatoid arthritis (RA), a chronic inflammatory disease, primarily attacks various synovial joints and certain extra-articular organs, such as pulmonary nodules [1], eyes [2], nervous system [2], kidneys [3], and so on. The occurrence of RA, which ranges from 0.5% to 2% among the general population, generally affects women in their forties and fifties, and is twice as likely to occur in women than in men [2].

RA patients are commonly treated according to the severity of the disease by using one or more of the following treatments at each visit. Escalation of therapy may proceed in a high disease activity state, and the most common treatments include methotrexate (MTX) with or without other conventional synthetic disease-modifying antirheumatic drugs (DMARDs) in further combination with biological agents. Sometimes, glucocorticoids [4, 5] may be used in severe uncontrolled cases. According to a study by Katerina C [6], the addition of glucocorticoids to MTX is usually more helpful than MTX monotherapy in early RA, and intramuscular and oral glucocorticoids were similarly effective as modes of bridging therapy. Furthermore, a combination of DMARDs is sometimes as effective as monotherapy with MTX while functional ability and radiographic progression are also taken into consideration [6].

A nonsteroidal anti-inflammatory drug (NSAID) relieves pain and stiffness but not the underlying causes of RA, while glucocorticoids blunt the immune response but cannot slow down the progression. The use of MTX and other DMARDs to slow disease progression is apparently beneficial [6], and since RA is a long-term autoimmune disease and occurs secondary to a loss of self-antigen tolerance, the advent of biologics therapies has demonstrated better outcomes [7, 8]. The addition of biologics to MTX therapy is usually favorable as well [6].

The use of biological agents has been associated with significantly increased rates of serious infections, including opportunistic infections and bacterial infections, in most studies [9], and the outcomes of adverse drug effects has resulted in most guidelines recommending biological agents to be used in patients who had responded poorly to or who were intolerant of one or more DMARDs [10]. According to one recent study [11],

autoantibodies and markers of systemic or local inflammation can be present long before clinical arthritis, and the disease process evolves long before the disease is clinically detectable, i.e., early treatment in RA patients should be associated with improved outcomes [11]. Furthermore, the use of NSAIDs and steroids are associated with increased cardiovascular events and infections, respectively [12, 13], and the use of methotrexate and other DMARDs may be associated with liver toxicity and gastrointestinal side effects, making early use of a biological agent a viable option. Currently, no published large-scale study has clarified whether early treatment of RA with a biological agent, based on the aforementioned reasons, leads to a better outcome. Therefore, the aim of this study was to evaluate the daily usage of glucocorticoids and painkillers, i.e. NSAIDs, in early treatment results of biologics compared to late biologics treatment of RA patients by using a population-based claims database in Taiwan.

Methods

Study design

This retrospective cohort study used the Taiwan National Health Insurance Research (NHIR) database from January 1, 1997 to December 31, 2013. Subjects are those RA patients who use biologics after 18 years old. The medication before and after 1 year of biologics will be recorded. We defined early use of biologics as biologics prescribed within 2.24 years after the RA diagnosis, and the late use of biologics was defined as those prescribed after 2.24 years of the RA diagnosis. These definitions are based on previous studies defining early arthritis as the onset of symptoms within 2 years of diagnosis [14-17], while we needed another 3 months for application biologics here in Taiwan, which equals a total of 2.24 years. We further defined the cut-off value of a 50% reduction in days of using DMARDs, steroids, or NSAIDs as the clinically meaningful tapering of medication [18], a protocol found in other studies.

Data source

Taiwan's National Health Insurance (NHI) Program began to be implemented on March 1, 1995. This program provides broad health insurance, and more than 99% of Taiwan's 23 million citizens have been included and received various healthcare services under this program, including physical therapy, inpatient and outpatient care, dental care, childbirth, Chinese medicine, etc. This NHIR provides information regarding hospitalization, epidemiological research, information on prescribed medication, diagnostic information, etc., all of which is considered high quality [19]. The NHIR randomly sampled a database of 1,000,000 subjects from all of its beneficiaries and database of subjects with major illnesses and has been releasing the data set to the public for studies since 1997.

Each person has been assigned a distinct identity number in the NHIR database, and identification data of the beneficiaries has been randomized to protect their privacy. This current study used the database of subjects with major illnesses and was financially supported by Kaohsiung Chang Gung Memorial Hospital, Taiwan (CMRP: CFRPG8H0231; IRB: 201801196B0).

Study cohort

The International Classification of Diseases, 9^{th}version (ICD-9) code was used for encoding diseases of interest. Patients aged at least 16 years old who were diagnosed with RA (ICD-9 code 714.0) in the NHI database at least three times in an outpatient department or at least one time in an inpatient department within 12 months were defined as RA patients in this study. RA patients who used one biological agent at least three times within 6 months to treat RA were defined as biologics users and have been included in this study starting from March 1997. We calculated the total days of prescribing NSAIDs, oral steroids, intra-articular steroid, MTX, and DMARDs by physicians. Furthermore, the overall medication prescribed days within 12 months before the initiation of biologics and 12 months following a one-month washout after discontinuation of a biological agent were recorded and analyzed. Exclusion criteria were as follows: the use

of a biological agent prior to diagnosis of RA; a diagnosis of ulcerative colitis (ICD-9 code 556.9, 556.8, 556) , Crohn's disease (ICD-9 code 555, 555.0, 555.1, 555.2, 555.9), psoriasis, and/or psoriatic arthritis (ICD-9 code 696.0, 696.1, 696.2, 6961, 696) within 5 years before the use of a biological agent [20]; RA patients who had never used any biological agent; and a follow-up period less than 12 months.

Statistical Analysis

We used t-tests and chi-square tests to compare baseline characteristics between these two groups. Logistic regression was used to estimate crude and adjusted odds ratios (OR) and 95% confidence intervals. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC).

Results

Demography data of study subjects

The ICD-9 coding of 714.0 found 49,690 RA patients among the NHI system data source. We excluded patients with missing data (n=20), under the age of 16 years old (n=1118) and dated before 2002 (n=22,318). We also excluded patients who had a concomitant diagnosis of ulcerative colitis, Crohn's disease, psoriasis, or psoriatic arthritis (n=90). After that, we picked up patients who had been prescribed biologics three times within six months with continuous treatment in outpatient clinics (n=4813). Among these patients, we further excluded one patient who used biologics prior to RA coding, 13 patients who used biologics only during hospitalization, and 125 patients who had expired during the follow-up period. Finally, we excluded those patients prescribed biologics after November 30, 2012 or before January 01, 1998. Overall, we included 821 RA patients in this study.

Among the 821 patients, 410 patients (50%) were classified in the Early group, and the other 411 patients (50%) were classified in the Late group (Table 1). Male RA patients had a higher ratio of receiving early treatment with biologics than female patients (Table 1, $p = 0.0379$). On the average, RA patients used biological agents for 2.89± 2.13 years. The age, income, living area (city or country), types of biologics, hepatitis B or C virus carrier, with or without chronic kidney disease, and heart failure diseases did not influence the timing of prescribing biologics for RA patients (Table 1, all $p>0.05$).

Comparison of prescribed days in one year before and after the biologics treatment.

The use of any of these three types of medication, including steroids, DMARDs, and NSAID was changed significantly after biologics treatment. Comparing 12 months before biologics, i.e., traditional treatment, and after the use of biological agents, oral medication significantly tapered after biologics compared to before biologics (Table 2, all $p <0.0001$), and the significance persisted even after study subjects were divided into early and late treatment ($p<0.0001$) (Table 2).

Duration of biologics treatment more than three-fourths of their length of traditional treatment reduces the prescribed days of steroid.

For patients who use biologics treatment more than three-fourths of their length of traditional treatment, we observed a decreasing trend of combinations of traditional treatments, DMARDs, NSAIDs, or steroids. The use of steroids, in particular, reached statistical significance (Table 3, $p<0.05$).

Biologics treatment contributes greatly to the reduced days of steroids and NSAID treatment.

Afterwards, we determined the odds ratio of each factor. The results show that men are 1.81 times more likely than women to taper oral glucocorticoids and NSAIDs. Younger age (<45) patients are 1.91 times more likely to taper steroids and NSAIDs than those aged over 65 years old. We found that RA patients receiving etanercept were 2.92 times more likely to taper oral medication, and those receiving adalimumab

tend to have a 2.88-fold greater tendency to taper oral medication than other biologics (all demonstrated in Table 4).

Discussion

Such factors as data collection interval, race, provider type (general physician vs. specialist), and type of drug coverage are associated with the use of DMARDs or biological agents among RA patients [10], and financial burden of certain expensive biological agents, usually leads to insufficient treatment among RA patients [10]. The data collection interval in this study was between 1998 and 2012, and during which period, the most available biologics agents for RA were etanercept (etanercept was available in Taiwan was since May 12, 2005) and adalimumab (adalimumab was available in Taiwan was since Aug 19, 2008). All the other currently available biologic agents for RA were neither available nor reimbursed by health insurance during the interval. Considering the study method, the cumulative dosage of analgesics for treating lower back pain has been reported in a previous study [21]. This similar method of cumulative days of administering a certain drug was applied in this present study to appropriately represent the severity of RA, since the medications were entirely reimbursed by Taiwan's health insurance, and all the medications prescribed are recorded and could be processed in the future, as in this study. Therefore, this study focused on the changes of cumulative days of the three aforementioned types of oral medication within 12 months before and after biological agents in the same RA patient. As a result, we were able to evaluate whether the use of a biological agent could taper the subsequent cumulative days of the aforementioned medications.

The most frequent causes of death in RA patients are cardiovascular disease, neoplasms, and sepsis [22], but none of these were considered as a covariate in this study because treatment of these diseases is irrelevant to the aforementioned medication, and we excluded patients that had passed away during the follow-up period. We focused on comparing cumulative days of oral medication in the same individual.

Previous studies have suggested that both smoking [23] and genes [24] may be involved in increased RA severity. However, due to the limitation of the NIHR database, we could not include these two variables in this current study. Furthermore, temperature and humidity are also claimed to influence RA severity, with both sunny conditions and less humid conditions significantly lowering RA activity [25]. We believe that these factors have a limited influence in this study due to the similar climate cycle throughout Taiwan. One interesting finding that we did not show in our result is that some patients started use biologics agent before his adulthood, which is before 18 years old, which by definition was juvenile RA.

The footnote in Table 1, we mark the early use of biologics and late use of biologics as either before or after 2.24 years (equals to 27 months) diagnosis of RA, which we combine the idea of two-year treatment window of opportunity from previous recommendation and evidence [16, 17], and the real-world situation in Taiwan that all the reimbursement cases of biologics are required to be authorized first before the prescription of biologics, and the average processing period is around 3 months (0.24 years). These patients who use biologics agent within 2.24 years of diagnosis of RA are representatives those patients within 2-year treatment window of opportunity. Otherwise, if we pick up those patients treated with biologics with exact 2 years within diagnosis of RA, we might pick up those patients with only 1.76 years (21 months) of RA duration, which could exaggerate the results in Table 2, and make the comparison of oral medication 1 year before and after the use of biologics unreliable.

In Table 3, we demonstrate the advantages between giving biological treatment in the first 2.24 years, compared to those who receive it later, which shows that the number of patients using glucocorticoids could be reduced significantly compared to the other group. ($p=0.047$) Those patients with delayed use of biologics have a tendency to increase use glucocorticoids. Despites of the statistics of difference of NSAIDs dose not reach significance, we still can see there is a trend of using more NSAIDs in those patients with delayed treatment with biologics ($p=0.06$). In delayed treatment subgroup, the NSAIDs tend to be prescribed more; 236 patients (57.42% of overall 411 patients) were having more than 75% of NSAIDs prescription days even

after treated with biologics. It gives us the hint that delayed treatment with biologics might hinder the process of tapering glucocorticoids and NSAIDs.[16, 26, 27]

Indication bias, comorbidities, and adherence rates (differences between oral prescribed agents and how much patients actually took) are listed as our study limitations. The reimbursement of biologics other than the Etanercept and the Adalimumab as first-line biologics treatment was not available in Rituximab and Tocilizumab by 2013, and the Golimumab was not available until the end of 2012, which could limit the case numbers in this research. Even though early treatment with an immune modulation agent has been proven to be beneficial in rheumatic patients, the adherence rates and comorbidities could be biased. However, due to increased risk of infectious diseases [28] to those with TB, have active or suspected infections, or easily get infected are not recommended to receive early full-dose DMARD agents and glucocorticoids treatment unless infections are under control.

Although biological agents have been considered appropriate pharmaceutical treatment for RA, immunological tolerance, which results in long-term remission, has not yet been established [29], despites several choices of biologics currently available. The search for alternative cures is still needed, and our study has provided some hints that early treatment with biologics may be a better choice than conventional oral medication, and this was the main purpose of our study.

We set the study period to 12 months prior to and 12 months following a one-month washout period after a biological agent in a bid to avoid such time varying covariates as adverse drug effects due to long-term use or progression of disease severity. Residence type (city/country), age, gender, community/nursing home, type of healthcare, and comorbidities [30] are commonly considered, and the current study focused on the efficacy of biologics and treatment timing by comparing changes of days of related drug administration in the same individual. Only gender and age were found to be independent factors that could decrease days of prescription of both steroids and NSAIDs in early use of biologics agents, preferentially Etanercept and Adalimumab after three months' treatment. This study indicates that younger patients only need short-term (2.53 ± 1.92 years, $p=0.03$) and early treatment with biologics (within 2.24 years of diagnosis of RA) in order to taper steroids and NSAIDs to less than 50% than before biologics treatment. This result has an important clinical implication that reflects updated treatment guidelines to use steroids at the lowest dose possible [31].

Limitations

The study is a retrospective research, and it has all the limitation that this kind of research should have. For example, missing data, coding bias, loss follow up patients, different inclusion status of patients and different treatment result in the end are all inevitable limitations. On the other hand, it is based on a Taiwan National Health Insurance Research database, which is reflecting only current medical and economic situation under particular situation and in particular time interval. This is a small piece of real-world evidence demonstrated to the world that the early treatment with biologics could cut oral medication in half in just two years. Nevertheless, no other objective evidence could be provided to demonstrate the efficacy of the biologics which is also another limitation in this study. This also affects the statistical analyses of the results. Furthermore, the reimbursement of biologics other than the Etanercept and the Adalimumab as first-line treatment of RA was not available in Rituximab and Tocilizumab, and the Golimumab was not available in Taiwan until the end of 2012. All of which could limit the case numbers treated by the biologics other than the Etanercept and the Adalimumab.

Besides, disease activity, genes and smoking may be involved in RA long term treatment efficacy, which all these three factors cannot be direct evaluated in this study. For example, we only calculated the decrease in treatment in 50% of the days, but there are no cumulative doses in each category of medication. The situation is similar between two groups, which we consider these issues contribute equally to each subgroup and may not affect the final comparison result. Also, by decreasing the use of oral treatment (NSAIDs and glucocorticoid), it could only mean a symptomatic effect and not necessarily have an effect on the activity or

accumulated damage of the disease (it is a bias not to have activity measures such as DAS28 or radiographic damage on this national database analysis). Not having measurements of poor prognosis factors such as serology, persistent activity, smoking, extra-articular manifestations and adherence to treatment limit the results in this large nation-wide study.

It is therefore possible that a minor portion of the included patients with RA were misdiagnosed from other types of arthritis, such as seronegative arthritis. However, we have done all the effort to minimize this entire situation by confirm the diagnosis with treatment medication. Unfortunately, the data in the medical records did not include enough information to assess the RA patient functional class and is why we omitted this parameter in the statistical analyses.

Conclusions

Early treatment of RA patients with biologics could minimize the prolonged usage of both glucocorticoids and NSAIDs is proved in this retrospective cohort study with national insurance database. The best timing of initiation biologics found in this study is within 2.24 years of diagnosis RA. Both gender and age were found to be independent factors that could decrease days of prescription of both steroids and NSAIDs in early use of biologics agents, such as Etanercept and Adalimumab. This result has an important clinical implication that reflects updated treatment guidelines to use steroids at the lowest dose possible, compare between those patients use biologics and those not.

References

1. Huret, B., et al., *[Pyopneumothorax in rheumatoid arthritis].* Rev Mal Respir, 2017.

2. Das, S. and P. Padhan, *An Overview of the Extraarticular Involvement in Rheumatoid Arthritis and its Management.* J Pharmacol Pharmacother, 2017. **8** (3): p. 81-86.

3. Mori, S., et al., *Prevalence of and factors associated with renal dysfunction in rheumatoid arthritis patients: a cross-sectional study in community hospitals.* Clin Rheumatol, 2017. **36** (12): p. 2673-2682.

4. Nagaraj, S., et al., *Early Rheumatoid Arthritis Presentation, Treatment and Outcomes in Aboriginal Patients in Canada: A Canadian Early Arthritis Cohort Study Analysis.* Arthritis Care Res (Hoboken), 2017.

5. Buttgereit, F., et al., *Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology.* Ann Rheum Dis, 2002.**61** (8): p. 718-22.

6. Chatzidionysiou, K., et al., *Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis.* 2017.**76** (6): p. 1102-1107.

7. Sharif, K., et al., *Physical activity and autoimmune diseases: Get moving and manage the disease.* Autoimmun Rev, 2017.

8. Scott, L.J., *Tocilizumab: A Review in Rheumatoid Arthritis.*Drugs, 2017. **77** (17): p. 1865-1879.

9. Singh, J.A., et al., *Adverse effects of biologics: a network meta-analysis and Cochrane overview.* Cochrane Database Syst Rev, 2011(2): p. Cd008794.

10. Gaitonde, P., L.M. Bozzi, and F.T. Shaya, *Factors associated with use of disease modifying agents for rheumatoid arthritis in the National Hospital and Ambulatory Medical Care Survey.* Semin Arthritis Rheum, 2017.

11. van Steenbergen, H.W., et al., *Preventing progression from arthralgia to arthritis: targeting the right patients.* Nat Rev Rheumatol, 2017.

12. Lin, T.C., et al., *Comparative Risk of Cardiovascular Outcomes Between Topical and Oral Nonselective NSAIDs in Taiwanese Patients With Rheumatoid Arthritis.* J Am Heart Assoc, 2017. **6** (11).

13. Turesson, C., *Comorbidity in rheumatoid arthritis.* Swiss Med Wkly, 2016. **146** : p. w14290.

14. Santos, H., et al., *Effectiveness of early adalimumab therapy in psoriatic arthritis patients from Reuma.pt - EARLY PsA.* Acta Reumatol Port, 2017. **42** (4): p. 287-299.

15. Ceccarelli, F., et al., *Remission in early, aggressive rheumatoid arthritis: a multicentre prospective observational Italian study ARPA (Artrite Reumatoide Precoce Aggressiva).* Clin Exp Rheumatol, 2013. **31** (3): p. 341-9.

16. Burgers, L.E., K. Raza, and A.H. van der Helm-van Mil, *Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives.* RMD Open, 2019. **5** (1): p. e000870.

17. Coffey, C.M., et al., *Evidence of Diagnostic and Treatment Delay in Seronegative Rheumatoid Arthritis: Missing the Window of Opportunity.* Mayo Clin Proc, 2019. **94** (11): p. 2241-2248.

18. van Mulligen, E., et al., *Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: first-year results of the randomised controlled TARA study.* Ann Rheum Dis, 2019. **78** (6): p. 746-753.

19. Lee, Z.M., et al., *Correlation of symptomatic enterovirus infection and later risk of allergic diseases via a population-based cohort study.* Medicine (Baltimore), 2017. **96** (4): p. e5827.

20. Lathia, U., E.M. Ewara, and F. Nantel, *Impact of adherence to biological agents on health care resource utilization for patients over the age of 65 years with rheumatoid arthritis.* Patient Prefer Adherence, 2017. **11** : p. 1133-1142.

21. Chin-Hung Chen, V., et al., *Factors affecting lumbar surgery outcome: A nation-wide, population-based retrospective study.* J Affect Disord, 2017. **222** : p. 98-102.

22. Pedersen, J.K., et al., *Mortality and its predictors in patients with rheumatoid arthritis: a Danish population-based inception cohort study.* Scand J Rheumatol, 2018: p. 1-7.

23. Chang, K., et al., *Smoking and rheumatoid arthritis.* Int J Mol Sci, 2014. **15** (12): p. 22279-95.

24. Shafia, S., et al., *Rheumatoid arthritis and genetic variations in cytokine genes: a population-based study in Kashmir Valley.* Immunol Invest, 2014. **43** (4): p. 349-59.

25. Savage, E.M., et al., *Does rheumatoid arthritis disease activity correlate with weather conditions?* Rheumatol Int, 2015.**35** (5): p. 887-90.

26. Quinn, M.A. and P. Emery, *Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention.* Clin Exp Rheumatol, 2003. **21** (5 Suppl 31): p. S154-7.

27. Contreras-Yanez, I. and V. Pascual-Ramos, *Window of opportunity to achieve major outcomes in early rheumatoid arthritis patients: how persistence with therapy matters.* Arthritis Res Ther, 2015. **17** : p. 177.

28. Ramiro, S., et al., *Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis.* Ann Rheum Dis, 2014. **73** (3): p. 529-35.

29. Hashimoto, M., et al., *Factors associated with the achievement of biological disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: the ANSWER cohort study.* Arthritis Res Ther, 2018. **20** (1): p. 165.

30. Grijalva, C.G., et al., *Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases.* JAMA, 2011. **306** (21): p. 2331-9.

31. Smolen, J.S., et al., *EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update.* Ann Rheum Dis, 2017. **76** (6): p. 960-977.

Hosted file

Table 1 characteristics of RA pt.pdf available at https://authorea.com/users/362059/articles/483311-comparison-of-glucocorticoids-and-painkiller-prescribed-days-between-rheumatoid-arthritis-patients-receiving-early-and-late-treatment-with-a-biological-agent-via-a-population-based-cohort-study

Hosted file

Table 2 Changes of days of receiving oral.pdf available at https://authorea.com/users/362059/articles/483311-comparison-of-glucocorticoids-and-painkiller-prescribed-days-between-rheumatoid-arthritis-patients-receiving-early-and-late-treatment-with-a-biological-agent-via-a-population-based-cohort-study

Hosted file

Table 3 the trend of days of receiving oral medication.pdf available at https://authorea.com/users/362059/articles/483311-comparison-of-glucocorticoids-and-painkiller-prescribed-days-between-rheumatoid-arthritis-patients-receiving-early-and-late-treatment-with-a-biological-agent-via-a-population-based-cohort-study

Hosted file

Table 4 Crude and adjusted odds ratio.pdf available at https://authorea.com/users/362059/articles/483311-comparison-of-glucocorticoids-and-painkiller-prescribed-days-between-rheumatoid-arthritis-patients-receiving-early-and-late-treatment-with-a-biological-agent-via-a-population-based-cohort-study