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Delay in biologic therapy and patient outcomes in patients with rheumatological conditions

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Abstract

Data (age, gender, diagnosis, dates of infusion therapy, flare status, impact on Activity of Daily Living (ADL), level of swelling, level of pain and stiffness) collected on patients who received abatacept infusion therapy between Aug 5, 2020 to Aug 4, 2022 was extracted from the Electronic Health Records system. Delayed versus on-time infusion therapy visits were compared with respect to observed decline in patient outcomes measures. A delay in therapy was estimated as a percentage delay (in days) from the FDA recommended schedule of administration at 0, 2, and 4 weeks, and every 4 weeks thereafter. Percentage of visits >33%, >50%, >100% and >200% delay were estimated.The visits with >100% delay showed consistently higher rates of worsened flare status (25.0% versus 10.9%), pain intensity (38.3% versus 20.9%), swelling (25.6% versus 20.2%), stiffness (31.8% versus 21.7%) and impact on ADL (12.5% versus 10.9%) compared to on-time visits. Thus, the delayed administration deviation from the labeled schedule was associated with worsened patient outcomes. A prolonged delay was associated with statistically significant negative impact across a broad range of end-points. The results can be used by rheumatology nurses to educate patients on the importance of adherence to the biologic therapy schedule so as to maximize the benefits from biologic therapies.

Keywords

Abatacept, Delayed patient visits, Delayed therapy, Delayed infusion therapy, Patient outcomes, Biologic therapy, Rheumatoid arthritis, Psoriatic arthritis, Inflammation, DMARD

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Introduction

Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) are both chronic diseases that often present with severe joint damage along with inflammation (1). RA affects the connective tissue in synovial joints, and the resulting inflammation impairs both movement and disability (2). The exact causes for RA are not fully understood; however, it is usually seen after infections and inflammation (2). PsA commonly affects the skin around the elbows and knees, but also adversely impacts peripheral and axial joints, entheses, other areas of the skin, nails, and causes swelling of the fingers and toes (3). Additionally, patients suffering from both diseases experience increased risk of cardiovascular disease, and rheumatoid arthritis patients can develop increased risk of infection or lymphomas (4,5). Both diseases are commonly found, with RA appearing in 1.3 million adults in the United States in 2014 (6), while psoriatic arthritis affects 20-30% of psoriasis patients and 2-4% of all adults (3). Often, DMARDs are the first palliative treatment option, but they are less effective in halting the progression of the disease and stopping joint deterioration (2). Various biologic therapies have emerged as treatment options in those cases where the disease is severe, or it has not responded to conventional DMARDs (2). Several biological therapies including adalimumab, certolizumab pegol, etanercept, golimumab, infliximab (TNF inhibitors); abatacept (T-cell co-stimulation modulator); rituximab (monoclonal anti-CD20 antibody); and tocilizumab and sarilumab (IL-6 inhibitors) are approved for use in patients with different rheumatological conditions including rheumatoid arthritis (RA), and psoriatic arthritis (PsA) (7-9).

Despite the well-documented benefits of biologic therapies in managing rheumatoid and psoriatic arthritis, ensuring adherence to recommended therapy administration schedules poses a significant challenge in clinical practice. Factors such as age, social support, gender, high costs, and adverse side effects can all negatively impact patients' adherence (10,11). Across different therapies used to treat RA and PsA, adherence and persistence rates ranged from 50-60% (12). Three studies reported a median abatacept adhrence rate of 52% (12). However, patient adherence is a key factor is determining the success of biologic therapies in managing RA and PsA, and is reported to triple the likelihood of patients achieving desired outcomes (11-13). Several studies have assessed adherence with anti-TNF agents in rheumatologic conditions (14-16), however, the impact of adherence on patient outcomes is not as well studied using real-world clinical practice data. Understanding the impact of treatment delays on patient outcomes is important for optimizing care delivery and improving overall treatment effectiveness (12,17-19). This study aimed to investigate the relationship between patient outcomes and delayed administration of one of the biologic therapies; abatacept. Abatacept regulates the stimulation of T-cells in order to block the production of inflammatory agents, such as TNF, interferon-γ, and interleukin-2 (2). In the long term, it prevents joint deterioration and has shown increased rates of remission in RA (20). Abatacept is recommended intravenously

at two-week intervals for the first four weeks and monthly thereafter (21).

This study aimed to investigate the relationship between the delayed administration of abatacept biologic therapy and patient outcomes among individuals with RA or PsA. The findings of this study hold significant implications for the management of patients with RA or PsA receiving biologic therapy; particularly abatacept. Demonstrating a significant association between delay in therapy administration and worsened patient outcomes would imply that treatment adherence is critical toward achieving optimal health outcomes. The results are anticipated to provide valuable insights for healthcare providers, emphasizing the need for strict adherence to recommended therapy schedules in order to maximize the beneficial effects of the therapy. Furthermore, possible trends; if found; would suggest that timely administration of abatacept biologic therapy is crucial for controlling the disease long-term and contributing to patient well-being.

Clinical Implications

The implications of this study extend beyond clinical practice to patient education and healthcare policies. Educating patients through doctor-patient conversations, nurse consultations, written materials such as brochures or pamphlets, educational videos, and educational workshops in clinics about the importance of adhering to their prescribed treatment schedule is important. This education ensures that patients are more proactive in managing their condition and potentially reduces the likelihood of treatment delays. Additionally, healthcare systems could benefit from implementing new strategies that would make therapy administration processes easier to access and minimize further barriers, including lengthy processes of obtaining medication authorization that contribute to delays.

Moreover, if delayed administration is found to be detrimental to patient outcomes, this would highlight the need for active monitoring and support for patients receiving biologic therapy, including possible reminders through apps or automated text messaging that would impress upon them the need to receive their treatment on time. By addressing delays in therapy administration and optimizing treatment adherence, healthcare providers can enhance the care delivered to patients with RA and PsA, ultimately improving their quality of life and reducing the short-term and long-term negative effects of the disease.

Methods

Study objectives

The study was designed to achieve the following objectives, 1] To demonstrate that a delay in biological therapy (abatacept) delivery for rheumatologic conditions may result in negative patient outcomes, 2] To determine if a greater delay in biological therapy delivery exacerbated the negative impact on patient outcome measures, 3] To identify patient outcome measures that were affected by a delay in the recommended therapy administration schedule.

Data on patients initiating abatacept infusion therapy in a Rheumatology clinic was extracted from the Electronic Health Records system.

Data extracted included patient age, gender, diagnosis, and dates of intravenous infusion therapy. Individual patient identifiers were not collected in order to maintain patient confidentiality.

Inclusion and exclusion criteria

Patients who received the first abatacept infusion therapy between August 5, 2020 and June 29, 2022 (treatment initiation period) were included in the study. Patients who received abatacept therapy within 1 year prior to the treatment initiation period were excluded in order to focus on those patients starting new treatment. In addition, patients who discontinued abatacept treatment before completing three therapy visits were excluded.

Patient outcome measures

Information on collected patient outcome variables included: flare status, impact on Activity of Daily Living (ADL) (yes, no), level of swelling, level of pain, stiffness (none, mild, moderate, severe). When pain, swelling, or stiffness were recorded on a scale of 1-10 in the chart, they were re-coded to Mild (0-3), Moderate (4-6) and Severe (7-10) for the purpose of analysis.

Adherence assessment

Delay in therapy was calculated as a percentage (in days) from the FDA recommended schedule of administration at 0, 2, and 4 weeks, and every 4 weeks thereafter.

Statistical analysis

The percentage of visits with >33%, >50%, >100% and >200% delay (which corresponded to 4, 7, 14, 28 days, respectively for a scheduled administration visit at 2 weeks, and 9, 14, 28, and 56 days, respectively for a scheduled administration visit at 4 weeks) were recorded. Delayed versus on-time infusion therapy visits were compared with respect to the rate of observed decline in patient outcomes measures. Statistical significance on differences in outcomes was tested using Spearman Correlation. Data were analyzed using SPSS.

Results

A total of 128 patients were identified as eligible for study inclusion; of these 81% were females.

Rheumatoid arthritis was the most common diagnosis (56.3%) followed by psoriatic arthritis (43.0%). These eligible patients contributed a total of 1103 abatacept infusion visits. For all the visits in the analysis, one third (33.2%) of 925 visits reported flares, and in 45.9% (of 912 visits) an impact on ADL was reported.

Table 1. Patient demographics

Demographic Characteristics	Delayed Administration*				On time Administration			
Delay (days[1]/days[2]), percent	(4/9) 33%	(7/14) 50%	(14/28) 100%	(28/56) 200%	(4/9) 33%	(7/14) 50%	(14/28) 100%	(28/56) 200%
N	153	121	55	19	822	854	920	956
Age Mean (years)	68.7	68.5	68.1	70	69.8	69.8	69.7	69.6
Female (N, (%))	129 (84.3%)	103 (85.1%)	50 (90.9%)	19 (100%)	646 (78.6%)	672 (78.7%)	725 (78.8%)	756 (79.1%)
Male (N, (%))	24 (15.7%)	18 (14.9%)	5 (9.1%)	0 (0%)	176 (21.4%)	182 (21.3%)	195 (21.2%)	200 (20.9%)
Ankylosing Spondylitis (N, (%))	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)	2 (0.2%)	2 (0.2%)	2 (0.2%)
Psoriatic Arthritis (N, (%))	55 (35.9%)	45 (37.2%)	16 (29.1%)	2 (10.5%)	338 (41.1%)	348 (40.8%)	377 (41%)	391 (40.9%)
Rheumatoid Arthritis (N, (%))	98 (64.1%)	76 (62.8%)	39 (70.9%)	17 (89.5%)	482 (58.7%)	504 (59.0%)	541 (58.8%)	563 (58.9%)

(days[1]/days[2]) measured for infusion intervals for 2 and 4 weeks respectively.

The distribution of Pain, Swelling, and Stiffness for all visits is summarized in Table 2.

Table 2. Distribution of Outcome Variables (Pain, Swelling, and Stiffness) for all visits

Outcome Measure	No (%)	Mild (%)	Moderate (%)	Severe (%)
Pain (n=951)	20.1	26.3	41.5	12.1
Swelling (n=877)	36.5	30.2	29.4	3.9
Stiffness (n=918)	18.7	32.2	41.2	7.8

The percent of patients with 1 to 20 visits ranged from 100% to 6.3% (Figure 1).

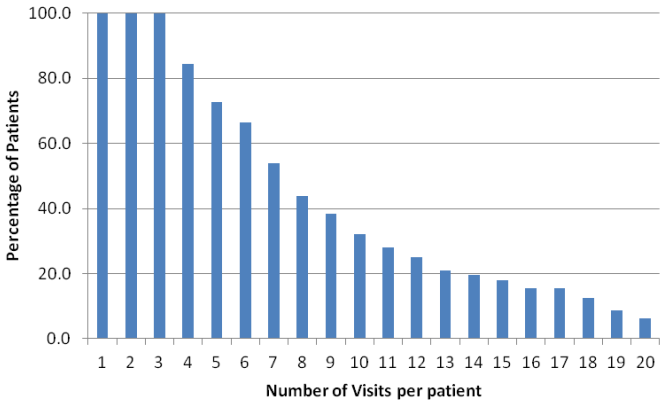

Figure 1. Distribution of patients by the number of visits (n=128)

Using the criteria of >100% delay in infusion therapy, of the 975 analyzable therapy administration visits, 5.6% (n=55) were delayed visits. The percentage of visits with worsened outcomes were consistently greater for visits with >100% delay versus on time infusion therapy administration (Figure 2).

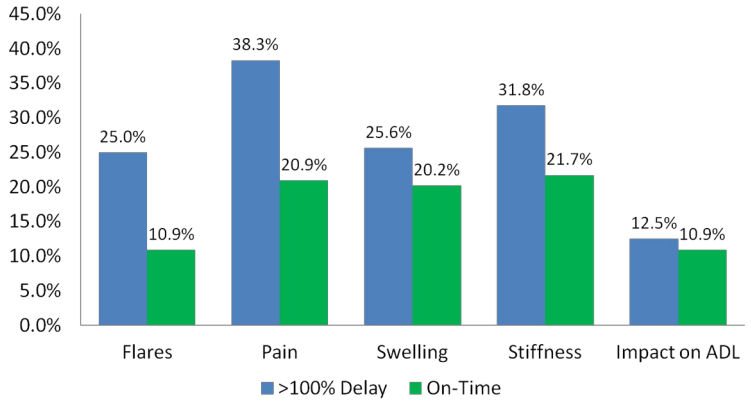

Figure 2. Percentage of visits with worsened patient outcomes (>100% delay)

In addition, consistently higher rates of worsened flare status, pain intensity, swelling, stiffness and impact on ADL compared to on-time visits were observed with a delay of >33%, >50%, >100% and >200% (Figures 3a, 3b, 3c, 3d, 3e).

The rates of worsened flare status, pain intensity, swelling, and stiffness generally increased with higher delay duration (Figures 3a, 3b, 3c, 3d). Statistical significance ($P<0.05$) for difference in flare status was achieved for all four delayed periods; for pain intensity for >100% and >200% delayed periods; for swelling and stiffness for >200% delayed period (Figures 3a, 3b, 3c, 3d).

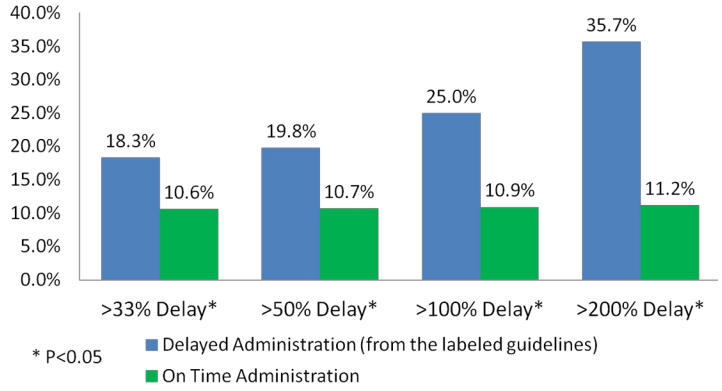

Figure 3a. Percentage of visits with worsened flare status

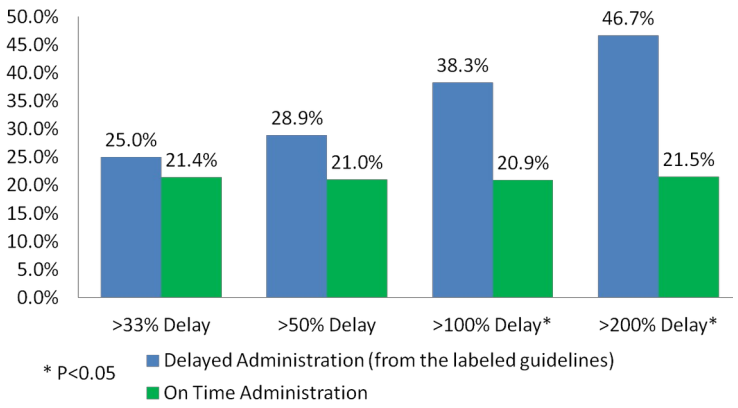

Figure 3b. Percentage of visits with worsened pain status

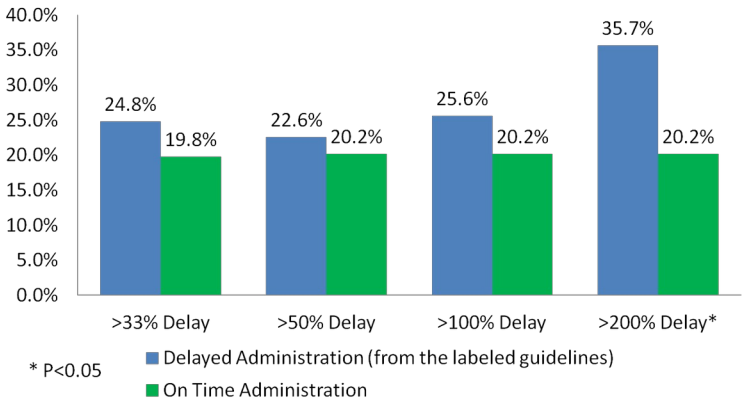

Figure 3c. Percentage of visits with worsened swelling status

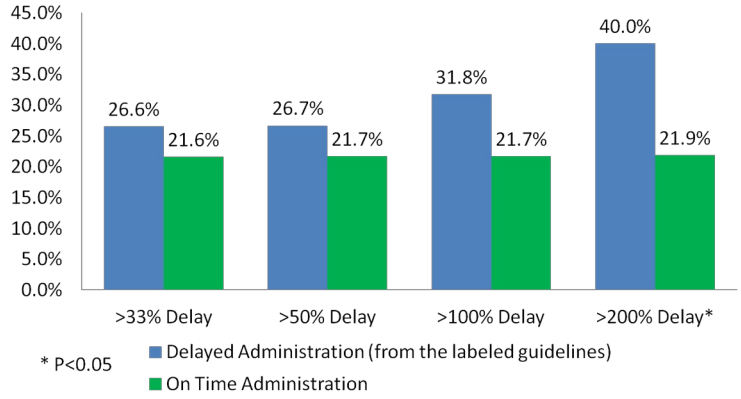

Figure 3d. Percentage of visits with worsened stiffness status

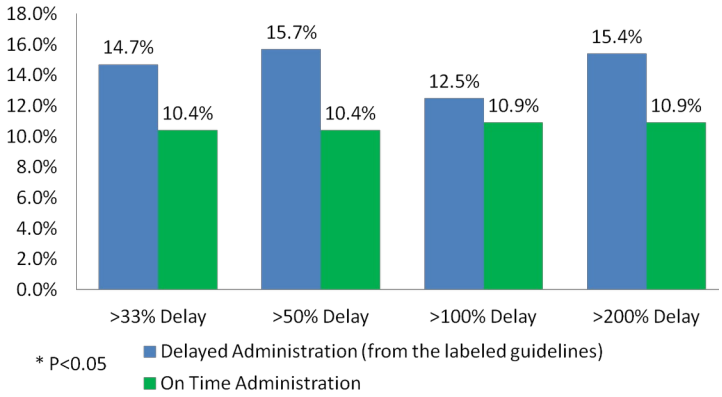

Figure 3e. Percentage of visits with worsened impact of ADLs

Discussion

Biologic therapies are a key therapy option in treating rheumatologic conditions. It is important to understand factors that impact the effectiveness of these therapies. The current study used real-world data from an outpatient clinic to examine the impact of not adhering to the labeled administration schedule on key patient outcomes in rheumatoid arthritis and psoriatic arthritis patients. The study results showed that delayed administration of a biologic therapy (abatacept) from the labeled schedule was associated with worsened patient outcomes.

The findings can be partly explained by the pharmacokinetic property of abatacept, having a terminal half-life about 13 days, and by the exposure-response relationship which showed trough concentrations of abatacept closely correlated with efficacy in RA patients (22,23). A delay in dosing or missed doses could decrease the minimum effective concentration in plasma hence resulting in impaired therapeutic effectiveness.

The results also showed that there was a trend of a greater proportion of visits with negative patient outcomes as the duration of delay increased. This trend was seen for flares, pain, swelling, and stiffness. These findings are important and useful to communicate to the patients about the importance of reducing any delay from the suggested biologic therapy administration schedule beyond what may be necessary due to factors including scheduled major surgery, COVID-19 related factors, or any other infections.

It is also important to understand which patient outcome is most sensitive to the delayed administration of biologic therapies. In this study, where patients received abatacept to manage their rheumatological conditions, flare status was the most sensitive patient outcome measure to delays from labeled administration schedule followed by pain intensity, swelling, and stiffness. In the study, impact on ADLs due to therapy delay did not achieve statistically significant difference. This may be due to a need for longer term patient-level data to see any potential changes in ADLs. Future research

should look at longer delays between follow-ups to examine the impact of longer therapy delay on these outcomes.

The current study is unique in its approach to conduct the analysis at the patient visit level. The results highlight that delays at the level of individual visits were associated with an impact on patient outcomes. Previous research has focused on understanding the patient characteristics and timely initiation of therapy (24). However, to our knowledge, this study is one of the few to understand the impact of delay at the individual visit level.

For the 100% delay, the female to male ratio was 9.98 and 3.71 for patients receiving delayed and on-time treatment respectively. However, since the effect of gender on the response and tolerance to abatacept was not significant (25), sex as a confounding variable for delayed treatment could be discounted. The placebo normalized response at 24 weeks was greater for patients with Rheumatoid Arthritis (RA) than with Psoriatic Arthritis (PsA) (26). Since the RA-to-PsA ratio was 1.7X greater in those patients who experienced delayed administration of the drug (70.9/29.1) to (58.8/41), a better outcome with regard to pain, swelling and stiffness would be skewed in favor of the delayed administration group. However, even with the odds of a better outcome skewed in favor of this group with regard to RA/PsA patients, it was observed that this group still presented with worse outcomes (as seen in Figure 2). This implied that the detrimental effects of the delayed administration of the drug outweighed any beneficial effects due to the increased RA/PsA patient ratio in the delayed administration group.

Limitations

A few data elements (e.g., time of first diagnosis) could not be collected due to a change in Electronic Health Records Systems in the clinic prior to study data collection. Time to first diagnosis can be an important variable to understand the patient population in the study. Due to smaller sample sizes, multivariate statistics could not be used to control for any potential confounding effects due to the observational nature of the study. The dose administered was not captured and neither was the weight or BMI. Whether the patient was concomitantly treated with TNF drugs (antitumor necrosis factor) or the patients had failed earlier regimens of Methotrexate or other non biologic DMARDS or Etanercept was not recorded.

The current study used anonymized data on abatacept infusion visits in an outpatient rheumatology clinic. There are a few areas where future research could supplement current research. This includes other therapies with different mechanisms of actions to examine the relationship between delay and patient outcomes. Including longer term patient outcome data would further strengthen the findings. Furthermore, we could not use well-accepted objective measures of disease, for example, ESR and CRP levels, which are used as biological markers for inflammation due to the nature of available data (27). Future research could include the impact of delay on these objective outcomes using longer term follow up data.

Conclusion

Delayed administration of a biologic therapy (abatacept) from the labeled schedule was associated with worsened patient outcomes. Furthermore, prolonged delay was associated with statistically significant negative impact across a broad range of end-points. The results can be used by Rheumatology Nurses to educate patients on the importance of adherence to biologic therapy schedule to maximize the benefits from biologic therapies.

The study's impact extends to patient education and healthcare policies. Informing patients about the importance of following their treatment plan can ensure they are more focused on managing their health and reducing delays in care. Healthcare systems could also adopt strategies to simplify therapy access and decrease those obstacles causing delays. The results highlight the need for vigilant monitoring and support for patients undergoing biologic treatments, including timely reminders. By minimizing treatment delays and improving adherence, healthcare providers can improve the quality of care for RA and PsA patients, and lessen the adverse effects of both diseases.

References

1. Merola, J. F., Espinoza, L. R., Fleischmann, R. (2018). Distinguishing rheumatoid arthritis from psoriatic arthritis. *RMD open*, 4(2), e000656, https://doi.org/10.1136/rmdopen-2018-000656

2. Chaudhari, K., Rizvi, S., Syed, B. A. (2016). Rheumatoid arthritis: current and future trends. *Nat Rev Drug Discov*, 15(5), 305-6, https://doi.org/10.1038/nrd.2016.21

3. Ocampo, V., Gladman, D. (2019). Psoriatic arthritis. *F1000Research*, 8, https://doi.org/10.12688/f1000research.19144.1

4. Taylor, P. C., Atzeni, F., Balsa, A., Gossec, L., Müller-Ladner, U., Pope, J. (2021). The key comorbidities in patients with rheumatoid arthritis: a narrative review. *Journal of clinical medicine*, 10(3), 509, https://doi.org/10.3390/jcm10030509

5. Li, L., Hagberg, K. W., Peng, M., Shah, K., Paris, M., Jick, S. (2015). Rates of cardiovascular disease and major adverse cardiovascular events in patients with psoriatic arthritis compared to patients without psoriatic arthritis. *JCR: Journal of Clinical Rheumatology*, 21(8), 405-410, https://doi.org/10.1097/rhu.0000000000000306

6. Hunter, T. M., Boytsov, N. N., Zhang, X., Schroeder, K., Michaud, K., Araujo, A. B. (2017). Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004–2014. *Rheumatology international*, 37, 1551-1557, https://doi.org/10.1007/s00296-017-3726-1

7. Chatzidionysiou, K. (2016). Optimizing biological treatments for rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, 45 (sup128), 64-75, https://doi.org/10.1080/03009742.2016.1208838

8. Mysler, E., Caubet, M., Lizarraga, A. (2021). Current and emerging DMARDs for the treatment of rheumatoid arthritis. *Open access rheumatology: research and reviews*, 13, 139-152, https://doi.org/10.2147/OARRR.S282627

9. Cantini, F., Niccoli, L., Nannini, C., Cassara, E., Kaloudi, O., Favalli, E. G., et al. (2016). Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis. In *Seminars in Arthritis and Rheumatism*, 45(5), 519-532, https://doi.org/10.1016/j.semarthrit.2015.10.001

10. Gadallah, M. A., Boulos, D. N., Dewedar, S., Gebrel, A., Morisky, D. E. (2015). Assessment of rheumatoid arthritis patients' adherence to treatment. *The American journal of the medical sciences*, 349(2), 151-156, https://doi.org/10.1097/maj.0000000000000376

11. Anghel, L. A., Farcaş, A. M., Oprean, R. N. (2018). Medication adherence and persistence in patients with autoimmune rheumatic diseases: a narrative review. *Patient preference and adherence*, 12, 1151-1166, https://doi.org/10.2147/PPA.S165101

12. Murage, M. J., Tongbram, V., Feldman, S. R., Malatestinic, W. N., Larmore, C. J., Muram, T. M., et al. (2018). Medication adherence and persistence in patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis: a systematic literature review. *Patient preference and adherence*, 12, 1483-1503, https://doi.org/10.2147/ppa.s167508

13. Goh, H., Kwan, Y. H., Seah, Y., Low, L. L., Fong, W., Thumboo, J. (2017). A systematic review of the barriers affecting medication adherence in patients with rheumatic diseases. *Rheumatology international*, 37, 1619-1628, https://doi.org/10.1007/s00296-017-3763-9

14. Mocanu, M., Toader, M. P., Rezus, E., Taranu, T. (2019). Aspects concerning patient adherence to anti-TNFα therapy in psoriasis: A decade of clinical experience. *Experimental and Therapeutic Medicine*, 18(6), 4987-4992, https://doi.org/10.3892/etm.2019.8008

15. Fayet, F., Fan, A., Rodere, M., Savel, C., Pereira, B., Soubrier, M. (2020). Adherence to subcutaneous anti-TNF treatment in chronic inflammatory rheumatism and therapeutic patient education. *Patient preference and adherence*, 14, 363-369, https://doi.org/10.2147/ppa.s240179

16. Salaffi, F., Carotti, M., Di Carlo, M., Farah, S., Gutierrez, M. (2015). Adherence to anti–tumor necrosis factor therapy administered subcutaneously and associated factors in patients with rheumatoid arthritis. *JCR: Journal of Clinical Rheumatology*, 21(8), 419-425, https://doi.org/10.1097/rhu.0000000000000320

17. Marengo, M. F., Suarez-Almazor, M. E. (2015). Improving treatment adherence in patients with rheumatoid arthritis: what are the options?. *International journal of clinical rheumatology*, 10(5), 345, https://doi.org/10.2217/ijr.15.39

18. Wong, P. K. (2016). Medication adherence in patients with rheumatoid arthritis: why do patients not take what we prescribe?. *Rheumatology international*, 36(11), 1535-1542, https://doi.org/10.1007/s00296-016-3566-4

19. Mena-Vazquez, N., Manrique-Arija, S., Yunquera-Romero, L., Ureña-Garnica, I., Rojas-Gimenez, M., Domic, C., Fernandez-Nebro, A. (2017). Adherence of rheumatoid arthritis patients to biologic disease-modifying antirheumatic drugs: a cross-sectional study. *Rheumatology International*, 37(10), 1709-1718, https://doi.org/10.1007/s00296-017-3758-6

20. Blair, H. A., Deeks, E. D. (2017). Abatacept: a review in rheumatoid arthritis. *Drugs*, 77, 1221-1233, https://doi.org/10.1007/s40265-017-0775-4

21. FDA. (2024). Highlights of Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125118s255lbl.pdf

22. Lutt, J. R. (2009). Efficacy, safety, and tolerability of abatacept in the management of rheumatoid arthritis. *Open Access Rheumatology: Research and Reviews*, 1, 17-35, https://doi.org/10.2147/oarrr.s4536

23. Li, X., Roy, A., Murthy, B. (2019). Population pharmacokinetics and exposure-response relationship of intravenous and subcutaneous abatacept in patients with rheumatoid arthritis. *The Journal of Clinical Pharmacology*, 59(2), 245-257, https://doi.org/10.1002/jcph.1308

24. Pappas, D. A., Kent, J. D., Greenberg, J. D., Mason, M. A., Kremer, J. M., Holt, R. J. (2015). Delays in Initiation of Disease-Modifying Therapy in Rheumatoid Arthritis Patients: Data from a US-Based Registry. *Rheumatol Ther*, 2(2), 153–164, https://doi.org/10.1007/s40744-015-0019-6

25. Nourisson, C., Soubrier, M., Mulliez, A., Baillet, A., Bardin, T., Cantagrel, A., et al. (2017). Impact of gender on the response and tolerance to abatacept in patients with rheumatoid arthritis: results from the 'ORA' registry. *RMD Open*, 3(2), e000515, https://doi.org/10.1136/rmdopen-2017-000515

26. Package Insert. (2024). Tables 9 and 13, https://packageinserts.bms.com/pi/pi_orencia.pdf

27. Lapić, I., Padoan, A., Bozzato, D., Plebani, M. (2020). Erythrocyte sedimentation rate and C-reactive protein in acute inflammation: meta-analysis of diagnostic accuracy studies. *American journal of clinical pathology*, 153(1), 14-29, https://doi.org/10.1093/ajcp/aqz142