Review of Published Literature Reporting Economic Burden of Treatment Switching in Rheumatoid Arthritis

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Background

- Rheumatoid arthritis (RA) is an incurable chronic inflammatory disease.
- American College of Rheumatology (ACR; Fraenkel, et al., 2021) and European League Against Rheumatism (EULAR; Smolen, et al., 2020) recommend treat-to-target approach, using disease-modifying antirheumatic drugs (DMARDs) and advise as many switches as necessary every three or six months to achieve the target.
  - Available therapies include:
    - Conventional-synthetic DMARDs: methotrexate, leflunomide, hydroxychloroquine sulfate, and sulfasalazine,
    - Biologic DMARDs (bDMARD):
      - Tumor necrosis factor inhibitors (TNFi): infliximab, adalimumab, golimumab, certolizumab, and etanercept,
      - Anti-interleukin-6 pathway antibodies (anti-IL-6): tocilizumab, sarilumab,
      - T cell co-stimulation inhibitors: abatacept,
      - B cell inhibitors: rituximab,
    - Janus kinase inhibitors (JAKi): tofacitinib, baricitinib, upadacitinib (in the US and EU) and filgotinib (in the EU).
- Within the Healthcare Effectiveness Data and Information Set (HEDIS), the National Committee for Quality Assurance (NCQA, 2023) monitors DMARD treatment rate in RA:
  - The measure reflects the number of adult health plan members who were diagnosed with rheumatoid arthritis (denominator) and who were dispensed at least one ambulatory prescription for a DMARD (numerator).
  - In 2018 (the most recent full data), the rates ranged 74%–88% (NCQA, 2023).
- Patients often fail to respond to a prescribed treatment; in which case the guidelines recommend switching therapy. ACR and EULAR recommend starting treatment with csDMARD and, in case of inadequate response, adding or switching to a TNF-α inhibitor.
- Prior research has reported that treatment switching is associated with increased economic burden, however a summary of such published literature is lacking.

Objectives

- We aimed to summarize published literature reporting economic burden of treatment switching in RA.

Methods

- **Table 1** outlines the methodological approach. In brief:
  - We used PubMed and desktop search to identify literature reporting healthcare resource use (HCRU) or costs associated with treatment switching in RA patients.
  - Keywords used: RA AND treatment switch* AND [HCRU OR cost]
  - Inclusion and exclusion criteria:
    - We included publications reporting healthcare resource use, costs, or both associated with treatment switching and compared with alterative outcomes: non-switching or discontinuation and continuation
    - We excluded publications reporting healthcare resource use and costs associated with treatment switching (switching from one mechanism of action to another) in comparison with treatment cycling (switching between drugs with the same mechanism of action) because such publications lacked the "no switch" option.

Table 1. Overview of Methodological Approach

Methodological Approach	Targeted Literature Review
Primary search conducted via	PubMed
Secondary search conducted via	General search via Google engine Google scholar References of identified articles
Timeframe	Last 10 years
Language	English
Scope	Abstracts and full-text manuscripts
Keywords	Rheumatoid arthritis Treatment switch* Cost OR healthcare resource utilization
Inclusion criteria	Publications reporting costs or healthcare resource use associated with switching in comparison with non-switching
Exclusion criteria	Publications reporting costs or healthcare resource use of treatment switching vs cycling

Results

- Eleven articles were selected for full text review after the following selection (**Figure 1**):
  - The PubMed search yielded 100 titles, 48 of which were selected for abstract review, 16 selected for full-text review (8 articles excluded as not relevant).
  - Three articles were identified via desktop search.
- The identified literature had the following characteristics:
  - Most studies were based on the US data (**Figure 2**);
  - Two articles reported data for RA combined with inflammatory conditions, and the rest reported data for RA alone;
  - Most articles published data for patients initiating a TNFi (n=3) or the next treatment after TNFi (n=3; **Figure 3**).
- Five articles reported 12-month treatment persistence: it ranged 45%-92% (**Figure 4**).
- Rates of switching (**Figure 5**):
  - Switching rates were reported consistently in most publications:
    - Most articles (n=9) reported treatment switch between 12% (Rashid, et al., 2016) and 18% (Degli Esposti, et al., 2017) per year.
    - One articles reported low 1-year switch rates: 7.8% (Messner, et al., 2014).
    - One article (Cannon, et al., 2016): high (28%) 1-year switch rate.
    - One article reported 2-year rates of switch: 30% of patients switching at least once, including 7% who switched twice.

Results

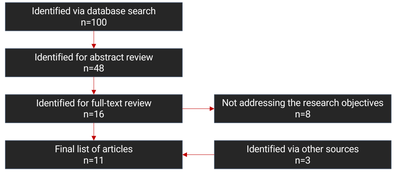

Figure 1. Flow of information

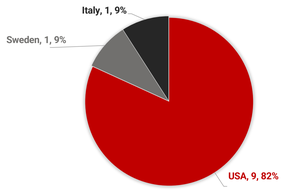

Figure 2. Geography of data origin

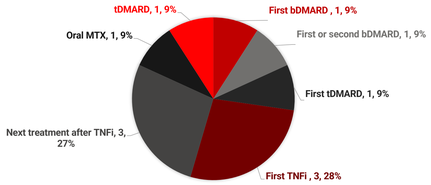

Figure 3. Treatments initiated by switchers

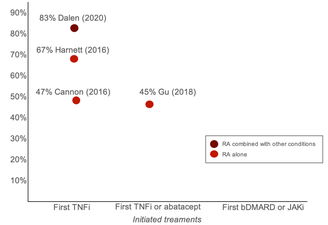

Figure 4. Treatment persistency 12 months post initiation

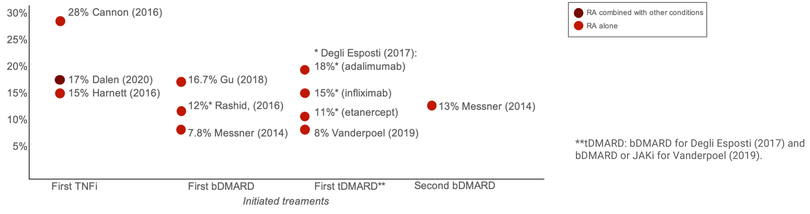

Figure 5. Reported rates of switching 12 months post initiation

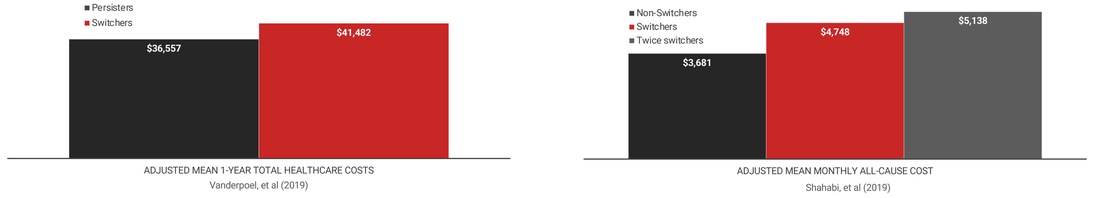

Figure 6. Reported adjusted costs in switchers vs comparison group

- Economic burden of treatment switching:
  - Ten publications reported costs associated with treatment switching:
    - Articles reported adjusted (n=6) or unadjusted (n=4) costs;
    - The articles compared cost in switching patients with:
      - Those who continued treatment (n=6), most often accompanied by treatment discontinuation,
      - Composite comparison group (n=4), e.g., "no switch," which could have included continued treatment or discontinuation.
    - Across all publications, the healthcare costs in switching patients were higher than in their comparison group (continued users or non-switchers):
      - The percent increase in adjusted mean healthcare costs was reported at 5% (Gu, et al., 2018), 24% (Hartnett, et al., 2016), 25% (Rashid, et al., 2016), and 51% for the 1st switch and 44% for 2nd switch (Messner, et al., 2014).
      - Shahabi, et al., (2019) reported adjusted mean monthly costs (**Figure 6**):
        - In patients who switched therapy at least once vs not switched:
          - All-cause: $4,785 (switches) vs $3,491 (non-switchers), p<0.001;
          - RA-related: $3,364 (switchers) vs $2,297 (non-switchers), p<0.001).
        - In patients who switched therapy twice vs non-switchers: $3,835 (switchers) vs $3,383 (non-switchers), p < 0.001).
- Three studies reported changes in HCRU associated with treatment switching.
  - Vanderpoel, et al. (2019) reported adjusted estimates (**Figure 6**) demonstrating that, in comparison with switching, continued biologic use was associated with:
    - Reduced healthcare visits: physician's office (−0.15, SS) or ED (−0.33, SS) visit, and inpatient admissions (-0.05, NS),
    - Increased use the pharmacy (0.27, SS).
  - Wolf, et al., (2017) reported that switching was associated with increased HCRU:
    - Patients with all inflammatory conditions, including RA had increased likelihood of hospitalization (aOR: 3.03*), emergency department use (aOR: 1.73, NS), outpatient visits (aOR: 1.05, NS) in comparison with treatment continuation,
    - Patients with RA reported increase in inpatient hospitalizations (aOR: 3.87, NS), emergency department visits (aOR: 6.94), and increased number of outpatient visits 1.09 (NS) outpatient visits.
  - Shahabi, et al. (2018) reported crude mean HCRU estimates:
    - Pre- and post-index means were statistically compared between switchers and non-switchers, however without accounting for baseline differences in cost or other patient characteristics,
    - A crude estimate of changes in HCRU (performed by author) indicated that switching was associated with either greater increase or smaller decline in HCRU in switchers than non-switchers, suggesting that switching was associated with increase in HCRU compared to non-switching.
- One article (Lee, et al., 2017) reported annual per-patient costs related to different types of HCRU in patients who continued oral methotrexate or switched to another therapy. The results showed that non-adjusted costs in different categories of switchers were higher than in continued users as related to hospitalizations, office visit, ED visits, and overall costs excluding pharmaceuticals.

Risk of Bias

- One article reported two-year risk of switching instead of the customary one-year. Such discrepancy in the reporting impedes comparison of outcomes across studies.
- Four articles reported cost or HCRU without adjustment for differences between groups. Given the non-experimental design of these retrospective studies, crude estimates present no opportunity to attribute the difference in HCRU or costs to switching. Due to the differences in patient characteristics (that were not balanced between groups by randomization), the difference in HCRU or cost may have been associated with patient characteristics other than treatments switching. Given that experimental design (e.g., randomization of patients into treatment continuation vs switching) would be unethical, adjusted real-world evidence estimates remain the best option for unbiased estimates in switchers vs non-switchers.
- Six articles compared reported results in a mixed group.
  - One article reported results for RA patients combined with other inflammatory conditions. This approach complicates the interpretation of results related to RA.
  - Five articles compared results in switchers with those in a mixed group: switchers and discontinuers (n=1) and non-switchers (could have included continuers and discontinuers; n=5)]
  - All literature combined bears a risk of publication of significant results, meaning that significant results reporting differences are more likely to be reported than results showing no difference. However, given the uniform consistency of the results, the risk of this type of bias is likely to be minimal.
    - The published studies had bias towards reporting data from US commercial databases (all prior to 2016), mostly biologic DMARD.
    - Few studies reported results from outside of the US.
    - No studies reported results for of Medicare or Medicaid.
  - One study reported the adjusted costs increment due to switching at 5% (Gu, et al., 2018), which stood out as outlier, inconsistent with the rest of the results 24% (Hartnett, et al., 2016), 25% (Rashid, et al., 2016) and 51% (Messnner, et al., 2014).

Conclusions, Discussions, Future Research

- Regardless of place therapy, between 12% and 18% (between one in eight and on one in six) of patients initiating a targeted DMARD switch their therapy within 1 year of initiation. These reports highlight challenges in the context of treat-to-target guidelines by EULAR and ACR.
- The proportion of treatment switches was reported for clinical practices between years 2003 and 2016. Therefore, these estimates are likely to represent an underestimate of switching in contemporary care (and the trends for the future) because:
  - (a) the range of approved and efficacious therapies has expanded over the last decade and
  - (b) the expansion in use of cost-effective biosimilar agents in recent years in many health economies has encouraged wide access to advanced therapies.
- Treatment switching presents economic burden in terms of increased healthcare resource and costs. In part this relates to the lack of biomarkers that reliably inform a management decision for the highest likelihood of treatment response that would attain the desired therapeutic target goal.
- Similar findings were illustrated by research focused on disease control in RA.
  - Grabner, et al., (2017), using validated claims algorithm, reported that only 30% of patients were classified as responders within 1st year of initiating a TNFi treatment. Non-responders had higher mean total all-cause medical costs and non-biologic pharmacy costs than responders.
  - Curtis, et al., (2022), using a linked data from electronic medical records and healthcare claims, reported that healthcare costs increased as disease activity progressed. The lowest costs were in patients who were in remission, followed by low disease activity and high disease activity.
- Further research is needed to understand the contemporary trends in and the burden of treatment switching, especially outside of the US and in US Medicare and Medicaid populations.
- All future research should consider the biases associated with previous publications and attempt to minimize bias by adjusting costs and HCRU estimates and explaining the rationale if results are reported for groups of patients combined.

Disclosures

PT: Consulting role for AbbVie, Aqtual, Inc., Biogen, Fresenius, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, Nordic Pharma, Pfizer, Sanofi, and UCB. Grant support from Galapagos; JA: Consulting role for Aqtual, Inc.; JG: Employment with Aqtual, Inc.;

References

- Cannon GW, et al. Adv Ther. 2016;33(8):1347-1359. doi:10.1007/s12325-016-0371-0
- Curtis, Jeffrey R et al.. doi:10.1007/s40744-022-00473-6
- Dalén J, et al. Adv Ther. 2020;37(9):3746-3760. doi:10.1007/s12325-020-01425-8
- Degli Esposti L, et al. Clinicoecon Outcomes Res. 2016;9:9-17. Published 2016 Dec 21. doi:10.2147/CEOR.S108730
- Fraenkel L, et al. Arthritis Care Res (Hoboken). 2021;73(7):924-939. doi:10.1002/acr.24596
- Grabner M, et al. Arthritis Res Ther. 2017;19(1):92. Published 2017 May 15. doi:10.1186/s13075-017-1293-1
- Gu T, et al. Am J Manag Care. 2018;24(8 Spec No.):SP338-SP345.
- Harnett J, et al. J Med Econ. 2016;19(2):91-102. doi:10.3111/13696998.2015.1099538
- Lee J, et al. Am Health Drug Benefits. 2017;10(1):42-49.
- Meissner B, et al. J Med Econ. 2014;17(4):259-265. doi:10.3111/13696998.2014.893241
- NCQA (2023) https://www.ncqa.org/hedis/measures/disease-modifying-anti-rheumatic-drug-therapy-for-rheumatoid-arthritis
- Rashid N, et al. J Med Econ. 2016;19(6):568-575. doi:10.3111/13696998.2016.1142448
- Shahabi A, et al. J Med Econ. 2019;22(4):350-358. doi:10.1080/13696998.2019.1571498
- Smolen JS, et al. Ann Rheum Dis. 2020;79(6):685-699. doi:10.1136/annrheumdis-2019-216655
- Vanderpoel J, et al. Clin Ther. 2019;41(6):1080-1089.e5. doi:10.1016/j.clinthera.2019.04.032
- Wolf D, et al. Clin Ther. 2017;39(4):849-862.e6. doi:10.1016/j.clinthera.2017.03.005

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