Article:
van Duren, BH, Wignall, A, Goodman, S et al. (3 more authors) (2022) The Effect of Perioperative Biologic Disease-Modifying Anti-Rheumatic Drugs on the Risk of Postoperative Complications. The Journal of Bone and Joint Surgery. ISSN 0021-9355

https://doi.org/10.2106/JBJS.21.00811

Title:

The Effect of Perioperative Biologic Disease-Modifying Anti-Rheumatic Drugs on the Risk of Postoperative Complications

Authors:

Bernard H van Duren*

Academic Clinical Lecturer Trauma and Orthopaedics, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

Alice Wignall

Research Fellow, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

Susan Goodman

Professor of Clinical Medicine, Weill Cornell Medicine; Director, Integrative Rheumatology and Orthopedics Center of Excellence; Medical Chief and Research Director, Combined Arthritis Program, Hospital for Special Surgery, New York, USA

Catherine Hewitt

Professor of Medical Statistics and Deputy Director of York Trials Unit, Department of Health Sciences, University of York, York, UK

Kulveer Mankia

Associate Professor of Rheumatology, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Hemant Pandit

Professor of Trauma and Orthopaedics, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

*Corresponding Author:

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, 2nd Floor Chapel Allerton Hospital, Chapeltown Rd, LS7 4SA.

b.h.vanduren@gmail.com

Conflicts of Interest:

The authors report no conflicts of interest related to this work. The authors alone are responsible for the content and writing of the paper.

Unrelated to this work, HP receives research support from Zimmer Biomet, DePuy Synthes, Pacira Pharmaceuticals, NIHR and holds consultancy contracts with Zimmer Biomet, DePuy Synthes, Smith and Nephew, Meril Life, Kennedy's Law, JRI Orthopaedics and Medacta

International. KM has consultancy with Abbvie, Lilly, UCB and grant income from Lilly and Gilead. SG receives research support from Novartis and consultancy with UCB.

Contributorship statement:

All authors contributed to conceptualisation, manuscript preparation and review. Searches were performed by AW, Data collection was undertaken by AW and BvD, Analysis was performed by BvD. Scientific advice provided by SG. Statistical analysis was supervised by CH. Manuscript preparation by BvD. Project supervision was led by KM & HP.

Acknowledgements:

Professor Pandit is a National Institute for Health Research (NIHR) Senior Investigator. Mr van Duren is a Leeds BRC-NIHR Academic Clinical Lecturer. The views expressed in this article are those of the author(s) and not necessarily those of the BRC, NIHR, or the Department of Health and Social Care.

We would like to thank Dr Andrea Conti and colleagues for providing additional data related to their prior publication.

Abstract:

Importance: Biologic disease modifying anti-rheumatic drugs (bDMARDS) are effective in treating inflammatory diseases, with increasing use over the past decade. These patients are at an increased risk of surgical site infection (SSI) when undergoing surgical procedures. The severe consequences of infection in orthopaedic surgeries has led to the practice of withholding bDMARDs peri-operatively. However, there is no definitive evidence showing a clear benefit of stopping bDMARDs, and in doing so patients may be at an increased risk of higher disease activity.

Objective: To compare the risk of infection, delayed wound healing, and disease flares associated with continuing or stopping bDMARDs in patients undergoing orthopaedic procedures.

Data Sources: We performed a systematic literature search of MEDLINE, EMBASE, and CENTRAL databases for studies comparing, continuing, or withholding bDMARDs in patients undergoing orthopaedic procedures.

Study Selection: Inclusion criteria were established following the PICO approach: Population: Patients on bDMARDs undergoing orthopaedic surgery. Intervention: Withholding bDMARDs. Comparator: Continuing bDMARDs. Outcomes: The outcomes were SSI, delayed wound healing, and disease flares.

Data Extraction and Synthesis: Titles and abstracts were screened prior to full text review. Overall Odds Ratio (OR) and associated 95% confidence intervals (CI) for pooled effects were calculated.

Results: 11 studies met the inclusion criteria; providing data from 2385 patients who continued and 4959 who stopped their bDMARDs peri-operatively. Continuing bDMARDs was associated with a significant lower risk of disease flares (OR= 0.22, 95%CI 0.05-0.95,

p=0.04), and non-significant increases in SSIs (OR=1.11, 95%CI 0.82-1.49, p=0.49) and wound complications (2.16, 95%CI 0.48-9.85, p=0.32).

Conclusions & Relevance: This meta-analysis highlights the limited evidence supporting the current practice of stopping bDMARDs peri-operatively. Our study suggests that patients may not be at an increased risk of developing infection or wound complications if bDMARDs are continued but are possibly at an increased risk of disease flare if bDMARDs are stopped. However, our conclusions are limited by the retrospective and heterogenous nature of the data, and possibly lack of study power.

Introduction:

Inflammatory rheumatic diseases are common systemic autoimmune conditions with rheumatoid arthritis (RA) prevalent in 0.5–1% and psoriatic arthritis (PsA) in 0.16%. of the general population(1,2). Over 400,000 people in the UK have RA, and in North America seven million people are affected, often with significant impact on quality of life(3). Conventional synthetic Disease Modifying Anti-Rheumatic Drugs (cDMARDs) such as methotrexate (MTX) and biologics (bDMARDs) such as tumor necrosis factor inhibitors (TNFi) are effective, well-established treatments for rheumatic diseases, which have dramatically improved outcomes. The use of bDMARDs is increasing, with up to 44% of RA patients undergoing joint arthroplasty taking bDMARDs at the time of surgery(4–6).

Patients with inflammatory arthropathies (IAs) are often more likely to undergo orthopaedic procedures, as these diseases are characterised by structural damage to joints and tissues(7,8). Although bDMARDs slow clinical and radiographic disease progression, they are associated with an increased risk of infection. Ito et al.(9) undertook a meta-analysis and found a slightly increased relative risk of surgical site infections in patients taking bDMARDs, but no increased risk of delayed wound healing after orthopaedic surgery. Overall, RA patients are at a 50%-80% greater risk of prosthetic joint infection than those with osteoarthritis(10–13).

Given the severe ramifications and difficulties in treating infections, the optimum management of bDMARDs during the perioperative period continues to be explored. Current guidelines advise clinicians to withhold bDMARDs pre-operatively(14,15). This introduces the potential risk of precipitating poor disease control (flare) with significant impact on the patient's overall well-being and quality-of-life. The trade-off between an increased risk of

infection while remaining on medication against the risk of suffering a flare with associated complications, can be challenging and requires collaboration between surgeons, rheumatologists, and patients. Flares are common among patients with RA and can be precipitated by medication withdrawal (16,17). Over 60% of patients with RA undergoing an arthroplasty have been shown to experience a flare(16).

To date, there is no clear evidence of whether/when to stop (and restart) bDMARDs during the peri-operative period with studies concluding that bDMARDs could be safely continued(18,19,20) and others reporting an increased risk of infection with continued use(21,22). Meta analysis(25) comparing patients continuing or withholding bDMARDs during the peri-operative period found a reduced risk of infection when stopping bDMARDs. This analysis was limited to data obtained from three studies. Further studies have been published since (20,26–31).

Previous studies have established an increased risk of infection in patients on bDMARDs compared to patients not on bDMARDs. The aim of this systematic review and meta-analysis, in contrast, was to compare the risk of surgical site infection (SSI), delayed wound healing, and disease flares in patients on bDMARDS who either continued or stopped taking them prior to undergoing orthopaedic surgery.

Methods:

Systematic review

The protocol for this review was created based on the PRISMA and AMSTAR 2 guidelines(32,33). MEDLINE, EMBASE, and CENTRAL databases were searched up to April 2021 to identify articles reporting the peri-operative use of bDMARDs in the context of orthopaedic surgery. The search strategies are outlined in Appendix A.

Inclusion criteria were established adhering to the PICO (Population Intervention Comparison Outcomes) approach:

- Population: Patients on bDMARDs undergoing orthopaedic surgery (mixed studies with >75% orthopaedic procedures considered eligible where orthopaedic procedures could not be separated).
- Intervention: Withholding bDMARDs during the peri-operative period
- Comparator: Continuing bDMARDs during the peri-operative period
- Outcomes: SSI (deep & superficial), delayed wound healing, and disease flare .

Only articles published in English were included. Titles and abstracts were screened for relevance prior to full full-text inspection by two independent investigators. Data were extracted using a standardised form. A third investigator was consulted regarding any discrepancies. The following data were recorded where available: a) Demographics: population studied, age, gender, procedure types b) Study design, country of origin, definition of infection, types and timing of bDMARDs stopping and restarting c) number of patients, infections, wound complications, and flares.

Analysis

158 The extracted data were analysed using Review Manager version 5.3 (Cochrane, London,
159 UK). Results from individual studies were pooled using the Mantel-Haenzel method. A fixed-
160 effects approach was used when the I^2 value was less than 25%; else a random-effects
161 approach was employed.

162

163 *Assessment of methodological quality & risk of bias*

164 Individual study quality for the included studies was assessed using Newcastle-Ottawa Scale
165 (NOS). Publication bias was assessed using a funnel plot. The overall quality of the evidence
166 in the meta-analyses was assessed using the Grading of Recommendations, Assessment,
167 Development and Evaluation (GRADE) system(34). Recommendations were classified as
168 either High, Moderate, Low, or Very Low (High = very confident that the effect in the study
169 reflects the actual effect, Moderate = quite confident that the effect in the study is close to the
170 true effect, but it is also possible it is substantially different, Low = the true effect may differ
171 significantly from the estimate, Very Low = the true effect is likely to differ significantly
172 from the estimate). This approach involved grading the evidence based on the following
173 criteria:

174 (1) Study Design: Randomised trial=high, Observational stud=low, Any other
175 evidence=very low
176 (2) Study Quality: Based on NOS scores.
177 (3) Inconsistency: Inconsistency of results assessment based on I^2 value (downgraded if I^2
178 > 25% indicating high heterogeneity)
179 (4) Indirectness
180 (5) Imprecision: Imprecision of results (downgrade applied if 95%CI did not exclude
181 baseline)

(6) Publication bias: Funnel plot analysis.

Source of Funding

No external funding source played a role in this investigation or preparation of this manuscript.

Results:

Included studies:

Eleven studies included data sets that met the criteria for inclusion (26–28,35–42). The PRISMA flowchart is shown in *figure_1*. Of these studies only a subset of the published cohorts met the inclusion criteria in six studies (26,35-38, 41).

Study Characteristics

No relevant RCTs were identified. All included studies were retrospective cohort studies, published between 2005 and 2020. Data of post-operative infection was available for all studies, wound complications (delayed healing, dehiscence) reported in three studies(27,28,37), and disease flares in four (26,40–42). However, data from one of the studies reporting flares could not be included in meta-analysis(26) due to insufficient data.

Patient Characteristics

7,344 patients (2385 continuing bDMARDs; 4959 stopping bDMARDs) were included (*Table_1*). The most common underlying diagnosis related to the use of bDMARDS was RA; other diagnoses included were PsA, psoriasis, juvenile arthritis, ankylosing spondylitis, and inflammatory bowel disease. TNF inhibitors were the most used bDMARDs although other modes of action including abatacept, rituximab, and ustekinumab were also included.

SSI:

There was an SSI in 3.06% (73/2385) of patients who continued their bDMARDS and 2.80% (139/4959) in those who had them withheld. The pooled OR for SSI was 1.11 (95%CI: 0.82-1.49) in favour of withholding bDMARDs, which was not significant (p=0.49) *(figure_2).*

Delayed wound healing:

There was delayed wound healing in 2.28% (19/833) of patients who continued their bDMARDS and 0.99% (13/1317) in those who had them withheld. The pooled OR for delayed wound healing was 2.16 (95%CI: 0.48-9.85) in favour of withholding bDMARDs, which was not significant (p=0.32) *(figure_3).*

Disease flares:

There was a flare in 7.32% (3/41) of patients who continued their bDMARDS and 25.71% (9/35) in those who had them withheld. The pooled odds ratio showed a significant decrease in disease flares when continuing bDMARDs: OR 0.22 (95%CI: 0.5-10.95) (p=0.04) *(figure_4).*

Arthroplasty

There was an SSI in 2.38% (46/1932) of arthroplasty patients who continued their bDMARDS and 2.32% (101/4345) in those who had them withheld. There was no significant difference in SSI noted when continuing or withholding bDMARDs in arthroplasty cases OR 1.01 [95%CI: 0.71-1.45] (p=0.95) (*Figure_5*).

Assessment of methodological quality & risk of bias:

All included studies were level IV evidence on the OCEBM scale. There was a wide variation in the quality of the studies(*Table_2*). A funnel plot representing the size of trials plotted against the effect size (Figure_6) showed an even spread confirming low risk of publication bias. GRADE analysis found the quality of evidence to be Very Low or Low for all analyses indicating a possibility that the true effect may differ significantly from the estimates presented.

Discussion:

The present meta-analysis is the first to comprehensively investigate the effect of withholding or continuing bDMARDs peri-operatively across inflammatory diseases in patients undergoing orthopaedic surgery. Our analysis did not demonstrate a significant difference in the risk of SSI in patients who continued vs stopped their bDMARDs during the peri-operative period as far as risk of infection or delayed wound healing was concerned in patients undergoing planned orthopaedic procedures. Conversely, there was a significant increase in disease flares when bDMARDs were withheld. It is important to note that the quality of studies identified was generally low.

DMARDs, both conventional and biological, aim to achieve disease remission or sustained low disease activity in patients with inflammatory disease. These patients are already at a higher risk of infection when undergoing surgery, which may further increase with the use of bDMARDs as they affect the host immune response. Previously, two meta-analyses have looked at the risks of SSI in patients on bDMARDs undergoing orthopaedic procedures. Goodman et al.(4) included studies of RA patients undergoing elective orthopaedic surgery, comparing 3681 patients with recent exposure (within 3 months of surgery) to TNFis (TNFi+) and 4310 with no recent exposure to TNFis (TNFi-) at the time of surgery. The TNFi+ group had higher risk of developing SSI compared with patients in the TNFi- group (OR 2.47, 95%CI 1.66-3.68, $P < 0.0001$). However, these cases are not comparable, as those requiring TNFi therapy likely have more severe disease, which is another known risk factor for infection (23,24). Ito et al.(9) also looked at RA patients undergoing elective orthopaedic surgery, showing a higher relative risk of SSI in patients using bDMARDs (OR 2.03, 95%CI of 1.40–2.96). Ito et al.(9) also looked at delayed wound healing, and found that use of bDMARDs does not increase the risk of delayed wound healing.

It is recognised that withholding bDMARDs can lead to an increased risk of disease flare which is characterised by pain and fatigue. Flare compromises patient rehabilitation following arthroplasty surgery. In addition, patients suffering from a flare commonly require corticosteroids, introducing an additional infection risk(1,43). It is therefore important to balance the risk of flares with the risk of infection if bDMARDs are continued in the perioperative period.

Current guidelines from the American College of Rheumatology (ACR) and American Association of Hip and Knee Surgeons (AAHKS) published in 2017 and The British Society for Rheumatology (BSR) published in 2019, advise clinicians to temporarily withhold biologic agents during the peri-operative period(14,15). The AAHKS guidelines (15) highlight that published evidence is of low quality and there is no clear evidence, in the form of a RCT, as to whether, or when, to stop bDMARDs. The evidence base used was in part extrapolated from non-surgical RCTs as well as input from a patient panel who strongly felt that the risk of infection outweighed the risk of flare. Since publication of the guidance, George et al. have published on large cohorts looking at the risk of infection associated with infliximab and abtacept when undergoing arthroplasty and concluded that withholding the drugs prior to surgery was not associated with an increased risk thus challenging this views(27,28).

Clay et al.(25) published the only meta-analysis to date comparing withholding to continuing bDMARDs prior to orthopaedic surgery. They looked at post-operative complications, SSI rate, and flares, comparing 1383 patients that withheld TNFi with 1360 patients continuing TNFi. They showed an increased risk of SSI in patients continuing TNF inhibitors (Risk Ratio

0.62, 95%CI 0.43-0.89). They also noted a significantly higher rate of disease flares in patients discontinuing TNFi (Risk Ratio 5.02, 95%CI 1.06-23.75). Our meta-analysis showed different results to those reported by Clay et al.(25) in that no significant difference in SSI was shown. We have included an additional six studies published in the intervening period of which the inclusion of the papers by George et al.(27,28) added a large number of patients comparing similar cohorts with clear bDMARD stop timing strengthening the current analysis. In addition, we only included the subset of patients in the study by Berthold et al.(35) who were actually on bDMARDs. We also excluded the data by Pettersson et al.(44) as this data was collected from the same institution over the same time period as that published by Berthold et al.(35) and as such we felt that this was duplicated data.

We identified four papers also reporting the impact of withholding bDMARDs on disease activity; three were included in the meta-analysis as flares attributed to orthopaedic procedures could not be inferred from the remaining paper(26). The included papers were small, low quality studies (40-42). The excluded paper, Bakkour et al.(26), reported on 42 patients with psoriasis and PsA undergoing various surgical procedures and found a significant increase risk of disease related flare in those withholding bDMARDs (40% vs 8.7%, p=0.003). More recently, Goodman et al.(16) recruited RA patients prior to arthroplasty surgery, and evaluated RA clinical characteristics 0 to 2 weeks before and 6 weeks after surgery. 120 patients were included in the final analysis, 51% of the cohort were on bDMARDS, all of whom had bDMARDs stopped and methotrexate (MTX) / glucocorticoid (GC) continued peri-operatively. 63% reported flares, of whom a higher percentage were treated with biologics (57% vs 42%, P=0.14). There was no difference in MTX or GC use on day of surgery between flares and non-flares. They also noted that patients with the highest risk of flare had higher disease activity at baseline. The authors concluded that although a

higher number of patients that discontinued medication flared, this was not an independent risk factor and therefore medication withdrawal was not associated with flares. However, this study was not designed to compare bDMARD continuation and discontinuation.

The current meta-analysis has certain limitations:

- The studies reviewed were observational, retrospective cohort studies in the absence of relevant RCTs. Many had a small sample size and only a small number reported delayed wound healing and flares.
- The definitions of infection as well as flares varied between studies, or were not provided, which may account for the differences in rates observed (*Table_3*).
- There was wide variation in the times that bDMARDs were withheld (*Table_1*). It is possible that this will hide significant risks in those patients who had their drugs stopped for a shorter period.
- Differences in dosages were not considered in this study on account of the data being too sporadic to achieve this. Differing risk profiles associated with higher/lower doses cannot be excluded.
- Not all the studies provided details of the concomitant use of cDMARDs and the confounding risk they may have for infection. Three studies did not discuss concomitant use of cDMARDs at all, so it is unclear as to whether this was included in the analysis of bDMARDs outcomes(37,41,42). Wendling et al.(40) reported how many patients were taking cDMARDs (MTX and GC), but did not mention whether this was taken into account in the analysis of bDMARDs outcomes. Scherrer et al.(36) did not define the cDMARDs prescribed and did not adjust for their co-founding effects, including them within the TNF outcomes. Others did not name the cDMARDs but adjusted for their cofounding effects in the analysis(26,27) whereas some authors

did record concomitant cDMARDs and adjusted for them in their analysis(35,38,39). The effect size of infection risk attributed to bDMARDs exposure may well have been over or underestimated owing to the concomitant cDMARDs use not being considered.

In conclusion, this meta-analysis did not demonstrate a significant increase in SSI or delayed wound healing in patients with a range of inflammatory conditions who continued bDMARDs peri-operatively. A significant increase in disease flares was noted in patients who had their bDMARDs withheld. Despite capturing data on a large number of patients, we remain cautious regarding the reliability of these data owing to the variable quality of the available studies and lack of randomised control trials. Furthermore, to our knowledge, there are no registered randomized control trials in progress which address this important question. The risk of developing a SSI when continuing bDMARDs peri-operatively should be weighed up against the risk of provoking a disease flare, which may subsequently require corticosteroids (with potential side effects including infection risk) and limit patient rehabilitation. RCTs are required to provide definitive answers in this important area.

References:

1. Gualtierotti R, Parisi M, Ingegnoli F. Perioperative Management of Patients with Inflammatory Rheumatic Diseases Undergoing Major Orthopaedic Surgery: A Practical Overview. Adv Ther. 2018 Apr 1;35(4):439–56.

2. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther. 2009;11(3):229.

3. Franco AS, Iuamoto LR, Pereira RMR. Perioperative management of drugs commonly used in patients with rheumatic diseases: a review. Clinics. 2017 Jun;72(6):386–90.

4. Goodman SM, Menon I, Christos PJ, Smethurst R, Bykerk VP. Management of perioperative tumour necrosis factor α inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis. Rheumatol Oxf Engl. 2016 Mar;55(3):573–82.

5. Goodman SM, Ramsden-Stein DN, Huang W-T, Zhu R, Figgie MP, Alexiades MM, et al. Patients with rheumatoid arthritis are more likely to have pain and poor function after total hip replacements than patients with osteoarthritis. J Rheumatol. 2014 Sep;41(9):1774–80.

6. Goodman SM, Johnson B, Zhang M, Huang W-T, Zhu R, Figgie M, et al. Patients with Rheumatoid Arthritis have Similar Excellent Outcomes after Total Knee Replacement Compared with Patients with Osteoarthritis. J Rheumatol. 2016 Jan;43(1):46–53.

7. Richter M, Crowson CS, Matteson EL, Makol A. Orthopedic Surgery among Patients with Rheumatoid Arthritis: A Population-based study to Identify Risk factors, Sex differences, and Time trends. Arthritis Care Res. 2018 Oct;70(10):1546–50.

8. Ward MM. Increased Rates of Both Knee and Hip Arthroplasties in Older Patients with Ankylosing Spondylitis. J Rheumatol. 2019 Jan 1;46(1):31–7.

9. Ito H, Kojima M, Nishida K, Matsushita I, Kojima T, Nakayama T, et al. Postoperative complications in patients with rheumatoid arthritis using a biological agent – A systematic review and meta-analysis. Mod Rheumatol. 2015 Sep 3;25(5):672–8.

10. Goodman SM, George MD. 'Should we stop or continue conventional synthetic (including glucocorticoids) and targeted DMARDs before surgery in patients with inflammatory rheumatic diseases?' RMD Open [Internet]. 2020 Jul 27 [cited 2021 May 21];6(2). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7722271/

11. Ravi B, Croxford R, Hollands S, Paterson JM, Bogoch E, Kreder H, et al. Increased Risk of Complications Following Total Joint Arthroplasty in Patients With Rheumatoid Arthritis. Arthritis Rheumatol. 2014;66(2):254–63.

12. Chen J, Cui Y, Li X, Miao X, Wen Z, Xue Y, et al. Risk factors for deep infection after total knee arthroplasty: a meta-analysis. Arch Orthop Trauma Surg. 2013 May;133(5):675–87.

13. Schrama JC, Fenstad AM, Dale H, Havelin L, Hallan G, Overgaard S, et al. Increased risk of revision for infection in rheumatoid arthritis patients with total hip replacements. Acta Orthop. 2015;86(4):469–76.

14. Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Rheumatology. 2019 Feb 1;58(2):e3–42.

15. Clinical Practice Guidelines Perioperative [Internet]. [cited 2021 May 21]. Available from: https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Perioperative-Management

16. Goodman SM, Mirza SZ, DiCarlo EF, Pearce-Fisher D, Zhang M, Mehta B, et al. Rheumatoid Arthritis Flares After Total Hip and Total Knee Arthroplasty: Outcomes at One Year. Arthritis Care Res. 2020 Jul;72(7):925–32.

17. Bykerk VP, Lie E, Bartlett SJ, Alten R, Boonen A, Christensen R, et al. Establishing a Core Domain Set to Measure Rheumatoid Arthritis Flares: Report of the OMERACT 11 RA Flare Workshop. J Rheumatol. 2014 Apr;41(4):799–809.

18. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot Ankle Int. 2004 May;25(5):331–5.

19. Johnson BK, Goodman SM, Alexiades MM, Figgie MP, Demmer RT, Mandl LA. Patterns and associated risk of perioperative use of anti-tumor necrosis factor in patients with rheumatoid arthritis undergoing total knee replacement. J Rheumatol. 2013 May;40(5):617–23.

20. Ito H, Tsuji S, Nakayama M, Mochida Y, Nishida K, Ishikawa H, et al. Does Abatacept Increase Postoperative Adverse Events in Rheumatoid Arthritis Compared with Conventional Synthetic Disease-modifying Drugs? J Rheumatol. 2020 Apr;47(4):502–9.

21. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Ustianowski AP, Helbert M, et al. Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011 Oct;70(10):1810–4.

22. Gaudiani MA, Winkelman RD, Ravishankar P, Rabah NM, Mroz TE, Coughlin DJ. The association of preoperative TNF-alpha inhibitor use and reoperation rates in spinal fusion surgery. Spine J Off J North Am Spine Soc. 2021 Feb 2;

23. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum. 2002 Sep;46(9):2294–300.

24. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002 Sep;46(9):2287–93.

25. Clay M, Mazouyes A, Gilson M, Gaudin P, Baillet A. Risk of postoperative infections and the discontinuation of TNF inhibitors in patients with rheumatoid arthritis: A meta-analysis. Joint Bone Spine. 2016 Dec;83(6):701–5.

26. Bakkour W, Purssell H, Chinoy H, Griffiths CEM, Warren RB. The risk of post-operative complications in psoriasis and psoriatic arthritis patients on biologic therapy undergoing surgical procedures. J Eur Acad Dermatol Venereol JEADV. 2016 Jan;30(1):86–91.

27. George MD, Baker JF, Hsu JY, Wu Q, Xie F, Chen L, et al. Perioperative Timing of Infliximab and the Risk of Serious Infection After Elective Hip and Knee Arthroplasty. Arthritis Care Res. 2017 Dec;69(12):1845–54.

28. George MD, Baker JF, Winthrop K, Alemao E, Chen L, Connolly S, et al. Timing of Abatacept Before Elective Arthroplasty and Risk of Postoperative Outcomes. Arthritis Care Res. 2019 Sep;71(9):1224–33.

29. Borgas Y, Gülfe A, Kindt M, Stefánsdóttir A. Anti-rheumatic treatment and prosthetic joint infection: an observational study in 494 elective hip and knee arthroplasties. BMC Musculoskelet Disord. 2020 Jun 29;21(1):410.

30. Tada M, Inui K, Sugioka Y, Mamoto K, Okano T, Kinoshita T, et al. Delayed wound healing and postoperative surgical site infections in patients with rheumatoid arthritis treated with or without biological disease-modifying antirheumatic drugs. Clin Rheumatol. 2016 Jun;35(6):1475–81.

31. Salt E, Wiggins AT, Rayens MK, Morris BJ, Mannino D, Hoellein A, et al. Moderating Effects of Immunosuppressive Medications and Risk Factors for Post-Operative Joint Infection Following Total Joint Arthroplasty in Patients with Rheumatoid Arthritis or Osteoarthritis. Semin Arthritis Rheum. 2017 Feb;46(4):423–9.

32. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

33. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339:b2535.

34. GRADE handbook [Internet]. [cited 2021 May 20]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

35. Berthold E, Geborek P, Gülfe A. Continuation of TNF blockade in patients with inflammatory rheumatic disease. An observational study on surgical site infections in 1,596 elective orthopedic and hand surgery procedures. Acta Orthop. 2013 Oct;84(5):495–501.

461 36. Scherrer CB, Mannion AF, Kyburz D, Vogt M, Kramers-de Quervain IA. Infection risk
462 after orthopedic surgery in patients with inflammatory rheumatic diseases treated with
463 immunosuppressive drugs. Arthritis Care Res. 2013 Dec;65(12):2032–40.

464 37. BONGARTZ T, HALLIGAN CS, OSMON DR, REINALDA MS, BAMLET WR,
465 CROWSON CS, et al. Incidence and Risk Factors of Prosthetic Joint Infection After
466 Total Hip or Knee Replacement in Patients With Rheumatoid Arthritis. Arthritis Rheum.
467 2008 Dec 15;59(12):1713–20.

468 38. den Broeder AA, Creemers MCW, Fransen J, de Jong E, de Rooij D-JR, Wymenga A, et
469 al. Risk factors for surgical site infections and other complications in elective surgery in
470 patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a
471 large retrospective study. J Rheumatol. 2007 Apr;34(4):689–95.

472 39. Ruyssen-Witrand A, Gossec L, Salliot C, Luc M, Duclos M, Guignard S, et al.
473 Complication rates of 127 surgical procedures performed in rheumatic patients receiving
474 tumor necrosis factor alpha blockers. Clin Exp Rheumatol. 2007 Jun;25(3):430–6.

475 40. Wendling D, Balblanc J-C, Brousse A, Lohse A, Lehuede G, Garbuio P, et al. Surgery in
476 patients receiving anti-tumour necrosis factor alpha treatment in rheumatoid arthritis: an
477 observational study on 50 surgical procedures. Ann Rheum Dis. 2005 Sep;64(9):1378–9.

478 41. Fabiano A, De Simone C, Gisondi P, Piaserico S, Lasagni C, Pellacani G, et al.
479 Management of patients with psoriasis treated with biological drugs needing a surgical
480 treatment. Drug Dev Res. 2014 Nov;75 Suppl 1:S24-26.

481 42. Talwalkar SC, Grennan DM, Gray J, Johnson P, Hayton MJ. Tumour necrosis factor
482 alpha antagonists and early postoperative complications in patients with inflammatory

joint disease undergoing elective orthopaedic surgery. Ann Rheum Dis. 2005 Apr;64(4):650–1.

43. Subramanian V, Pollok RCG, Kang J-Y, Kumar D. Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. Br J Surg. 2006 Jul 1;93(7):793–9.

44. Pettersson E, Geborek P, Gu¨lfe A.TNF Blockade during Elective Orthopaedic and Hand Surgery in Arthritis Patients: Friend or Foe? Arthritis & Rheumatism. 2010 Oct; Vol. 6 2, No. 1 0 (Supplement): S574

Figures:

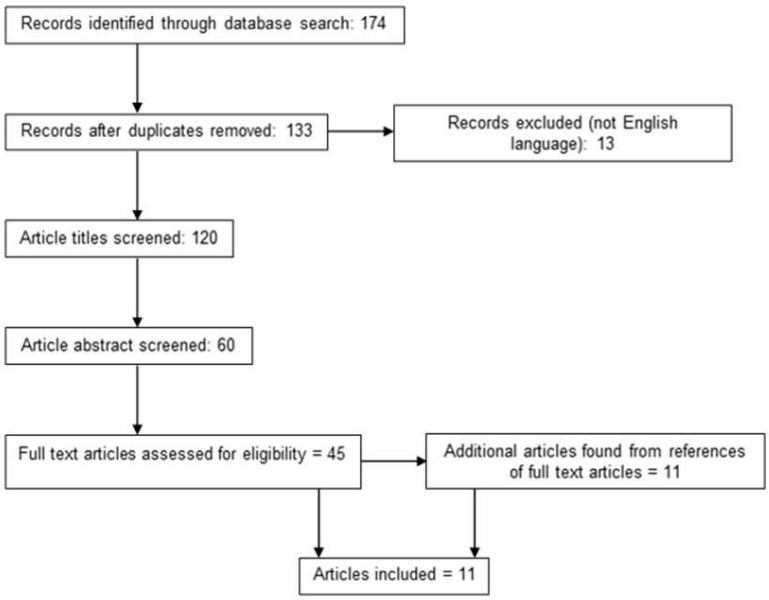

Figure 1: *PRISMA style flowchart corresponding to article selection for the meta-analysis.*

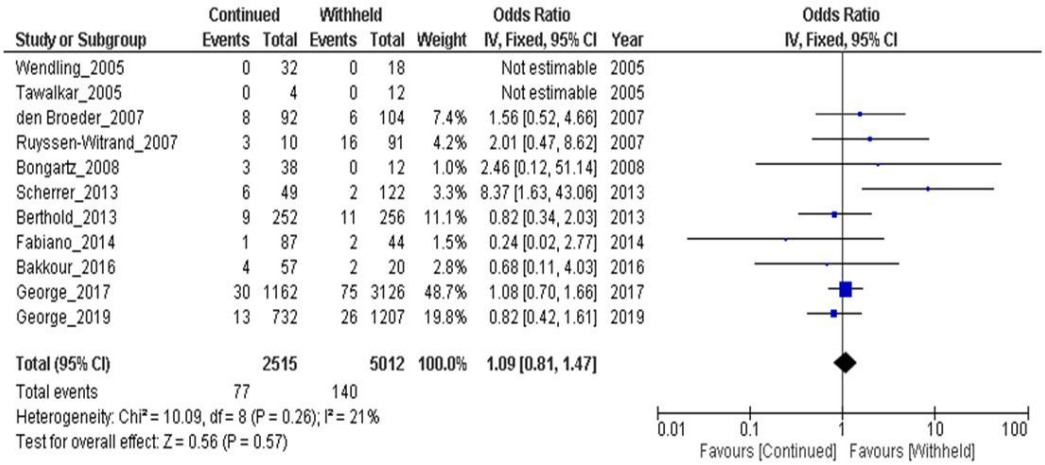

Figure 2: *Forest plot representing the odds ratio of post-operative infections between*

patients continuing or stopping bDMARDs. Two studies(40,42) *did not report any events of infection and as such did not contribute to the overall meta-analysis.*

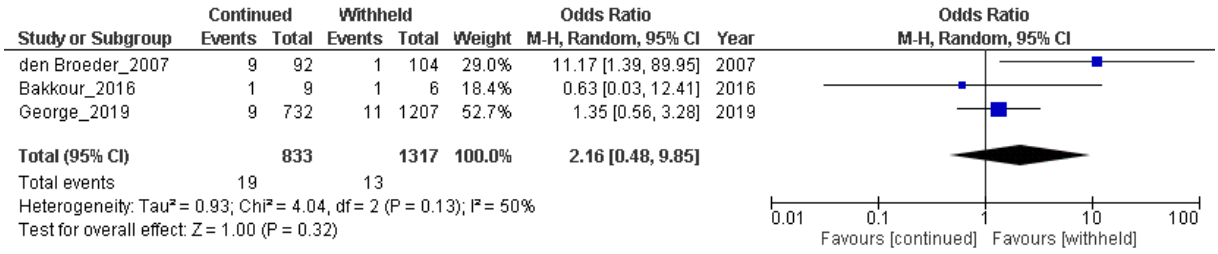

Figure 3: *Forest plot representing the odds ratio of delayed wound healing between patients continuing or stopping bDMARDs.*

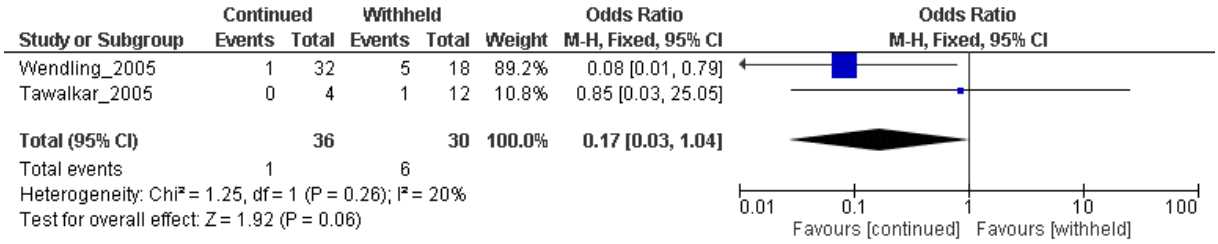

Figure 4: *Forest plot representing the odds ratio of disease flares between patients continuing or stopping bDMARDs.*

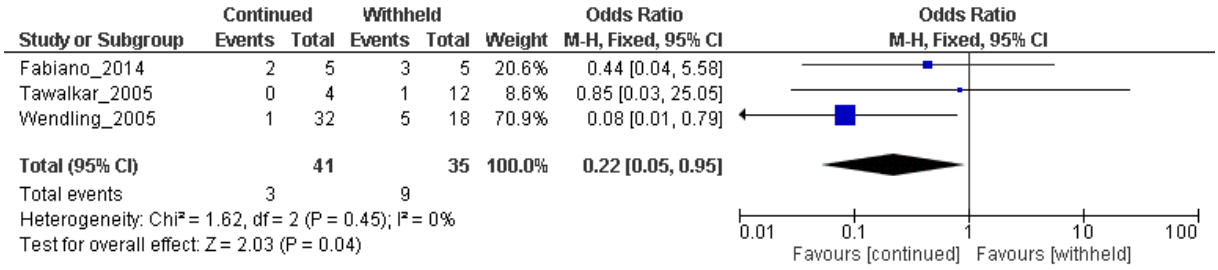

Figure 5: *Forest plot representing the odds ratio of post-operative infections between patients who underwent hip & knee arthroplasty whilst continuing or stopping bDMARDs*

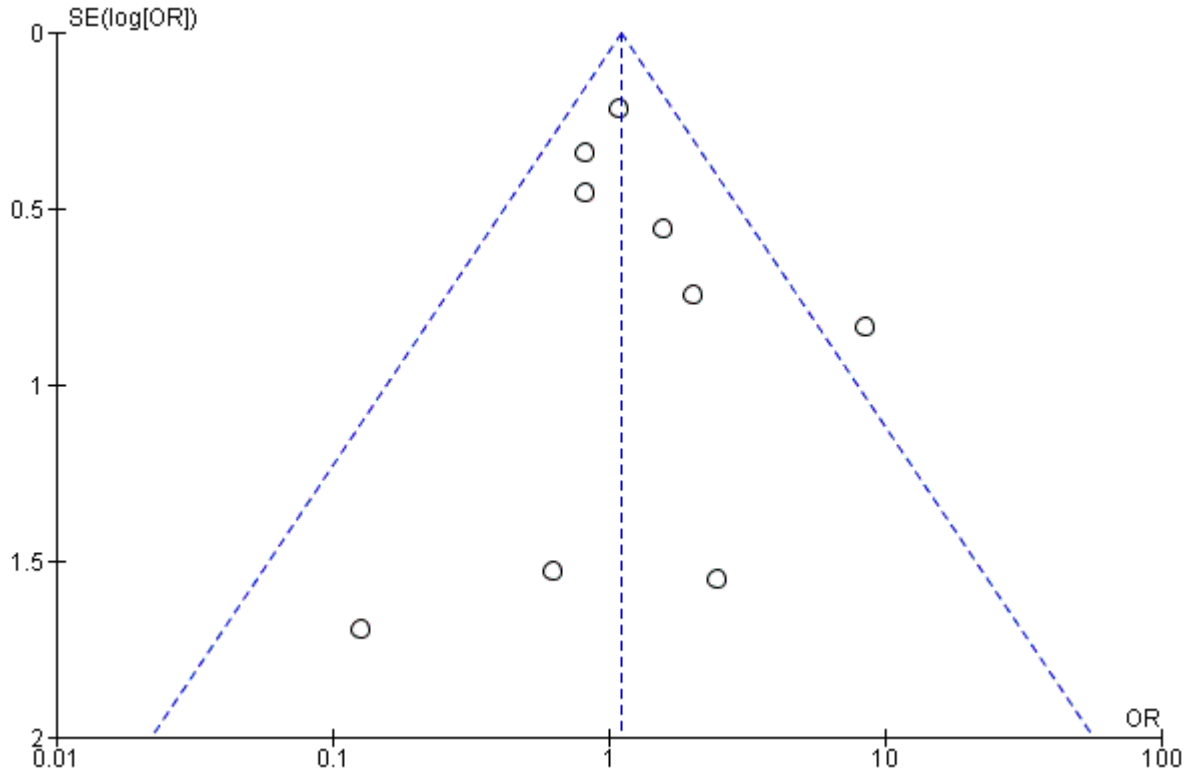

Figure 6: *Funnel plot for SSI meta-analysis giving a graphical representation of a likely low risk of publication bias.*