EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2021.21027

Original Article

How well are biologic and conventional DMARDs tolerated in psoriatic arthritis: A real world study

Issrah I. Jawad, Muhammed K. Nisar

Abstract

Objective: Even though disease-modifying antirheumatic drugs (DMARDs) are well established in routine clinical practice, longitudinal real-world data for their retention and tolerability are sparse, especially in psoriatic arthritis (PsA) patients. Our objective was to describe the characteristics of our large PsA cohort including the comorbidities and evaluate real-world DMARD tolerability and discontinuation rates with reasons for stopping treatment.

Methods: We retrospectively interrogated the electronic, multipurpose, live setting database at our university hospital to identify 335 patients diagnosed with PsA who had received conventional DMARDs (cDMARDs) and/or biologic DMARDs (bDMARDs) between 1994 up to and including April 2019.

Results: In total, 170 (50.7%) patients had discontinued one or more cDMARDs prior with a mean duration before discontinuation of 9.9 months. In contrast, only 28 (24.8%) patients had stopped a course of bDMARDs at some point. The mean duration before biologic therapy was discontinued was 18.2 months.

Conclusion: To our knowledge, this is the first dedicated retrospective review of a large real-world PsA cohort addressing drug survival and tolerability of DMARDs over a 20-year period. Our study shows that in reality, cDMARDs are not well tolerated. This should encourage review of international guidance allowing earlier employment of biologics in the treatment paradigm.

Keywords: Drug tolerance, psoriatic arthritis, biologic therapy, DMARD

Introduction

Psoriatic arthritis (PsA) is a chronic seronegative inflammatory arthropathy with diverse phenotypes, including peripheral arthritis, enthesitis, dactylitis, and involvement of axial skeleton.[1] Increased prevalence of metabolic syndrome and cardiovascular disease are also well recognized among patients with PsA.[2] If left untreated, PsA can lead to joint deformities and disability with undesirable effects on quality of life and perhaps higher mortality.[3]

Considering the impact of PsA and the sea change in therapeutic landscape with unprecedented improvements now achievable, treatment-to-target has become the standard of management.[4] Thanks to the breadth of disease-modifying antirheumatic drugs' (DMARDs) armamentarium, remission and/or minimal disease activity state has been shown to be attainable in clinical practice.[4] Though biologics have been at the forefront of this revolution, all international guidelines such as The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and the European League against Rheumatic Diseases recommend conventional DMARDs (cDMARDs) to be the first rung of therapeutic ladder—particularly for peripheral arthritis.[5,6]

Despite the fact that both cDMARDs and biologic DMARDs (bDMARDs) are well established in routine clinical practice, longitudinal real-world data for their retention and tolerability are sparse. Limited such evidence is available for rheumatoid arthritis (RA).[2–4] However, PsA is a more heterogeneous disorder, with involvement in areas quite distinct from RA.[7] The PsA patient cohort is also known to have more cardiometabolic comorbidities[2] and consequently is more likely to be subject to the complications associated with polypharmacy. There are some reports of real-world methotrexate (MTX) and biologics discontinuation in PsA;[8,9] little literature exists in relation to the broader range of DMARDs employed to treat PsA.

Our objective was to describe the characteristics of our large PsA cohort including the comorbidities and evaluate real-world DMARD tolerability and discontinuation rates with reasons for stopping treatment.

ORCID iDs of the authors:
I. I. J. 0000-0002-4478-1721;
M. K. N. 0000-0002-5132-3972.

Cite this article as: Jawad II, Nisar MK. How well are biologic and conventional DMARDs tolerated in psoriatic arthritis: A real world study. *Eur J Rheumatol.* 2022;9(2):100-103.

Department of Rheumatology, Luton and Dunstable University Hospital NHS Foundation Trust, Luton, United Kingdom

Address for Correspondence: Issrah I. Jawad; Rheumatology Department, Luton and Dunstable University Hospital NHS Foundation Trust, Luton United Kingdom

E-mail: issrah.j@gmail.com

Submitted: February 3, 2021
Accepted: March 6, 2021
Available Online Date: January 21, 2022

Copyright©Author(s) - Available online at www.eurjrheumatol.org.

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Methods

As part of an audit at our university teaching hospital, we retrospectively interrogated the electronic, multipurpose, live setting database to identify all patients diagnosed with PsA who had received cDMARDs and/or bDMARDs between 1994 up to and including April 2019. All patients fulfilled ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria for PsA. We had access to full patient records including details on comorbidities, drugs, and disease management. Patients who had stopped treatment were then identified. The dose of respective drugs immediately prior to treatment withdrawal and the reason for discontinuation was noted. The duration of drug treatment was then calculated, and any discrepancy was clarified by the treating team. Reasons for drug withdrawal were further classified as follows:

- All gastrointestinal symptoms—including nausea, vomiting, diarrhea, abdominal pain or discomfort, dyspepsia, mucosal ulceration, bloating, and loss of appetite.
- All respiratory symptom—including breathlessness, cough, and lower and upper respiratory tract infections.
- Abnormal blood—such as thrombocytopaenia, elevation in alanine aminotransferase, anemia or alkaline phosphatase, or others.
- Neurological and psychological—including headaches, dizziness, depression, anxiety, sleep disturbance, and poor concentration.
- Fatigue—fatigue, tiredness, loss of energy, or feelings of being "washed out."
- Cutaneous—rash, ulceration, nodules, itching, and blistering.
- Alopecia.
- Fertility and family planning.
- Patient choice—drug stopped for personal reasons unrelated to the development of side effects, for example, lifestyle choice (particularly pertaining to alcohol intake), noncompliance with monitoring bloods, change of route request.
- Inefficacy.
- No longer indicated—completed treatment or clinical indication to stop, for example, commencement of treatment for cancer.

Main Points

- Longitudinal real-world data for retention and tolerability of DMARDs are sparse, especially in the psoriatic arthritis patient population.
- cDMARDs are not well tolerated compared to bDMARDs in our large PsA patient cohort.
- International guidelines that continue to recommend methotrexate and other cDMARDs as the initial choice of therapy for PsA should be revisited.

Ethics committee approval was received for this study from the Ethics Committee of Luton and Dunstable University Hospital NHS Trust (Approval Date: May 5, 2019; Approval number: 13/2019-20/Medicine/Rheumatology).

Statistical analysis

Statistical analysis was completed using Statistical Package for the Social Sciences (SPSS) version 27 (IBM Corp.; Armonk, NY, USA) with statistical significance being considered when $P < .05$.

Results

Our institute has a catchment population of over 350.000 patients from diverse ethnic backgrounds including a 40% Black, Asian and Minority Ethnic (BAME) population. We identified 335 patients with PsA; of which, 194 (58%) of the sample were female. Age ranged from 13 to 81 years with a mean age of 46 years. In total, 333 patients had a recorded ethnic background, with 264 (79%) White Caucasian patients, 58 (17%) Asian, four (1%) African-Caribbean, and seven (2%) other.

Two hundred and thirty (68%) of our patients also had concurrent skin psoriasis. Thirty (9%) patients in our cohort had diabetes, and 59 (18%) suffered from cardiovascular disease. Table 1 outlines further demographics and comorbidities.

Table 1. Cohort Demographics and Comorbidities

	N (%)
Demographics	
Ethnic background	
White Caucasian	264 (79)
Asian	58 (17)
African-Caribbean	4 (1)
Other	7 (2)
Not stated	2 (1)
Age	
<20 years	5 (1)
20-40	102 (30)
40-60	164 (49)
60-79	62 (18)
≥80 years	2 (1)
Comorbidities	
Psoriasis	
Yes	230 (68)
No	106 (32)
Diabetes	
Yes	30 (9)
No	305 (91)
Cardiovascular disease	
Hypertension	44 (13)
Hypercholoestrolemia	24 (7)
Ischaemic heart disease	11 (3)
Smoking	
Yes	34 (10)
No	120 (36)
Not stated	181 (54)
Depression	
Yes	26 (8)
No	309 (92)

cDMARDs discontinuation

Single cDMARD therapy was the current treatment for 161 (48%) of our sample as of April 30, 2019. Figure 1 shows the distribution across different cDMARDs used as part of sole or combined therapy.

Of the patients who had taken cDMARDs, 21 (10%) patients had trialed three or more different drugs. One hundred and seventy patients had stopped one or more courses of their

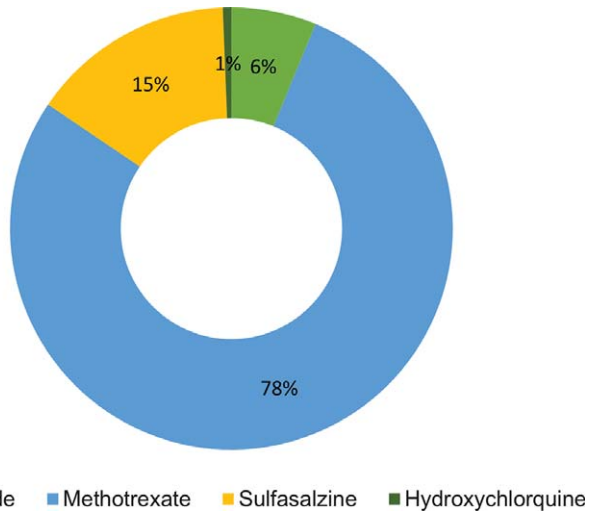

Figure 1. Current cDMARD drugs.

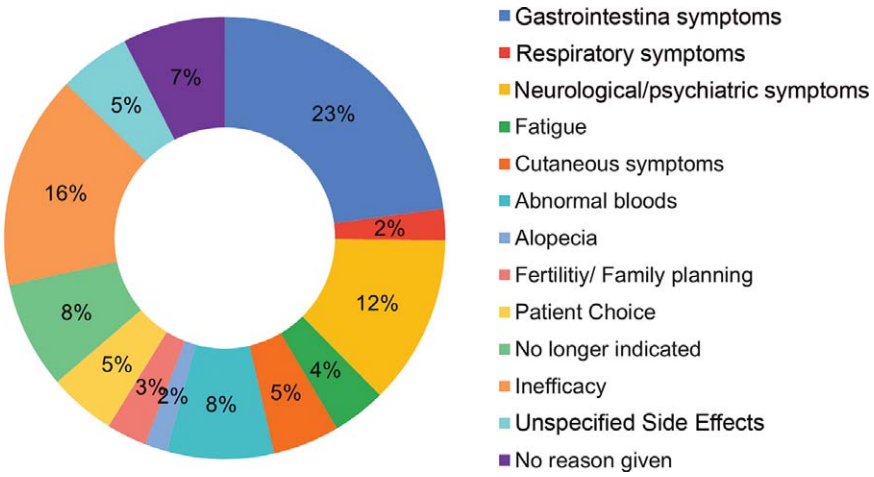

Figure 2. Reasons for discontinuation of cDMARDs. GI, Gastrointestinal; Resp, Respiratory; Neuro/Psych, Neurological/psychiatric; Unspecified SE, Unspecified Side Effects

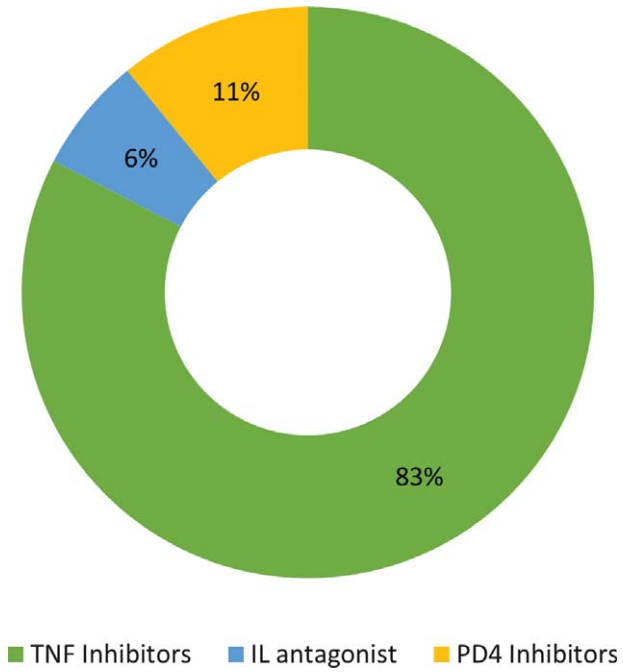

Figure 3. Current bDMARD drugs.

cDMARD treatment resulting in 278 discontinued courses; of which 158 (51.6%) were stopped due to side effects and 48 (15.7%) due to inefficacy. The mean duration before discontinuing a cDMARD was 9.9 months (4 days to 4.6 years). A breakdown of the reasons for discontinuation of cDMARDs is shown in Figure 2.

bDMARDs discontinuation

One hundred and thirteen (34%) patients had been treated with a bDMARD with 105 (93%) on active bDMARD treatment at the time of analysis. Sixty (18%) individuals were prescribed combination therapy of biologics and cDMARDs. Figure 3 shows the distribution of bDMARDs across our cohort.

Twenty-eight patients discontinued a total of 37 courses of prescribed bDMARDs with a mean duration before discontinuation of 18.2 months (8 days to 9.5 years). Fifteen (39.5%) were due to side effects and 13 (34.2%) due to inefficacy. Figure 4 shows the reason for discontinuation of bDMARDs.

Discussion

To our knowledge, this is the first dedicated retrospective review of a large real world PsA cohort addressing drug survival and tolerability of both cDMARDs and biologics over a 20-year period. One hundred and seventy (50.7%) patients had discontinued one or more cDMARDs prior with a mean duration before discontinuation of 9.9 months. In contrast, only 28 (24.8%) patients had stopped a course of bDMARDs at some point. The mean duration before the biologic therapy was discontinued was 18.2 months.

Our study shows that in the real world, cDMARDs are not well tolerated. These results are in accordance with a similar study from the UK, which also showed that MTX survival is poor in both RA and PsA.[9] On the other hand, both retention of biologic therapy are significantly better than cDMARDs. This concurs with similar studies in psoriasis[10] and RA[11] where biologics survival was found to be higher.

There have been similar results reported in the RA population, which may provide some general insights for the PsA population. For instance, Wabe et al.[12] found, in RA patients, that drug survival was as low as 34.8% in their existing cDMARD users despite showing that it was associated with significant reductions in their disease activity score-28 (DAS28).

A US Cohort of RA patients newly initiated on bDMARDs was found to have adherence rates of 46% for year 1 and 34% for 2 years.[13] A systematic review by Murage et al.[11] found rates of biologic compliance in RA as high as 90% but only identified one paper related to PsA patients which looked specifically at Golimumab.[8]

It is noteworthy that randomized controlled trials report lower discontinuation rate in cDMARDs arms of the studies; however, these trials are generally limited to 6 months hence likely underestimating the long-term discontinuation rates.[14] Furthermore, the recruits tend to be healthier with lower comorbidity and polypharmacy burden, thus not reflective of real-world patients.[15]

International guidelines continue to recommend MTX and other cDMARDs as the initial choice of therapy for PsA.[5,6] The treat to target approach in PsA,[16] thus, has serious implications as patients do not tolerate their medications. Hence, it is important for clinicians to recognize that cDMARDs therapy is not durable and, hence, requires careful shared decision-making to empower patients to share their drug-related concerns, so that the therapy can be escalated appropriately. Our analysis did not include patients who suffer from side effects but continue therapy, thereby impacting treatment adherence and hence the true scale of the issue is likely higher.

These findings have also confirmed that more restricted access to advanced therapy as

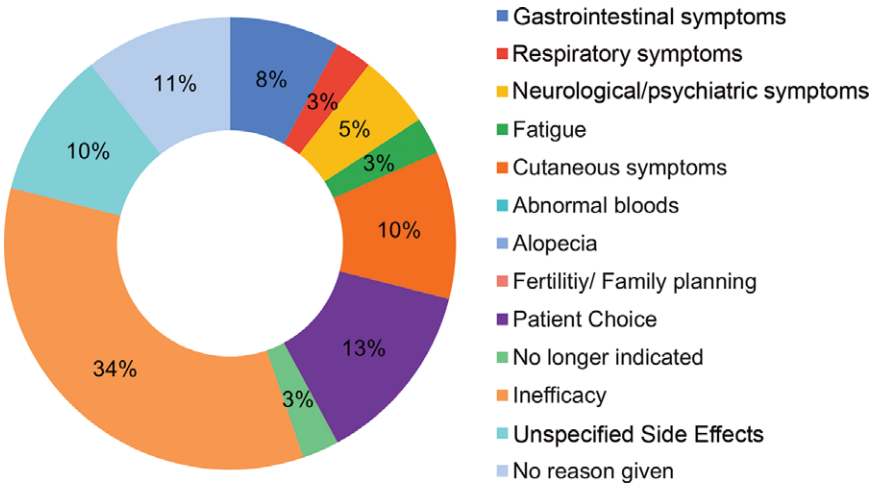

Figure 4. Reasons for discontinuation of bDMARDs.

stipulated by National Institute of Health and Care Excellence (NICE) that requires an adequate trial of two cDMARDs for 6 months prior to advanced therapy needs to be reviewed. This approach is unlikely to be cost effective as the disease progresses while patients struggle with cDMARDs prescription and, thus, delay biologics which are more likely to be tolerated and retained longer. Hence, there is an urgent need to revisit NICE guidance to allow earlier employment of biologics in the treatment paradigm with significant benefits to both patients and the health economy.

The lack of longitudinal data from PsA patients highlights the need for a national registry similar to what has been long established in RA. Guidelines and recommendations in PsA are made using experiences from the RA community, which are demographically and clinically different from the PsA cohort. Increasing the body of research on the real-world experiences of patients with PsA such as the PsA biologics register in the UK will help inform more effective recommendations for our PsA patients.

Our study has several strengths including a large sample of patients over a long period from a university hospital with a varied ethnic mix increasing its external validity in other PsA populations. Real-world data help appreciate the true extent of drug discontinuation, which may not be captured in short-term clinical studies with limited numbers of highly selected participants. The main limitation is the retrospective nature of the study; however, two authors independently assessed the data to limit bias. We were unable to look at potential confounders or evaluation of methods to improve tolerability. Despite these limitations, we feel the interrogation of such a large clinical database provides useful insight into real-life clinical practice in an area where so little research currently exists.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Luton and Dunstable University Hospital NHS Trust (Approval Date: May 5, 2019; Approval number: 13/2019-20/Medicine/Rheumatology).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.K.N., I.J.; Design - M.K.N., I.J.; Supervision - M.K.N., I.J.; Resources - M.K.N., I.J.; Materials - M.K.N., I.J.; Data Collection and/or Processing - M.K.N., I.J.; Analysis and/or Interpretation - M.K.N., I.J.; Literature Review - M.K.N., I.J.; Writing - M.K.N., I.J.; Critical Review - M.K.N., I.J.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

1. Coates LC, Tillett W, Chandler D, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. *Rheumatology*. 2013;52(10):1754-1757. [CrossRef]
2. Ferguson LD, Siebert S, McInnes IB, Sattar N. Cardiometabolic comorbidities in RA and PsA: Lessons learned and future directions. *Nat Rev Rheumatol*. 2019;15(8):461-474. [CrossRef]
3. McArdle A, Pennington S, FitzGerald O. Clinical features of psoriatic arthritis: A comprehensive review of unmet clinical needs. *Clinic Rev Allerg Immunol*. 2018;55(3):271-294. [CrossRef]
4. Coates LC, Conaghan PG, D'Agostino MA, et al. Remission in psoriatic arthritis—Where are we now? *Rheumatology*. 2018;57(8):1321-1331. [CrossRef]
5. Coates LC, Kavanaugh A, Mease PJ, et al. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheum*. 2016;68(5):1060-1071.
6. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis*. 2020;79(6):700-712.
7. Kavanaugh A. Psoriatic arthritis: Treat-to-target. *Clin Exp Rheumatol*. 2012;30(4):S123-S125.
8. Ellis L, Bolge S, Rice P. Golimumab utilization patterns and refill adherence in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. *Value Health*. 2014;17(3):A49-A50. [CrossRef]
9. Nikiphorou E, Negoescu A, Fitzpatrick JD, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: A retrospective review of discontinuation rates from a large UK cohort. *Clin Rheumatol*. 2014;33(5):609-614. [CrossRef]
10. Brunasso AM, Puntoni M, Salvini C, et al. Tolerability and safety of biological therapies for psoriasis in daily clinical practice: A study of 103 Italian patients. *Acta Derm Venerol*. 2011;91(1):44-49. [CrossRef]
11. Murage MJ, Tongbram V, Feldman SR, et al. Medication adherence and persistence in patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis: A systematic literature review. *Patient Prefer Adherence* 2018;12:1483-1503. [CrossRef]
12. Wabe N, Lee A, Wechalekar M, McWilliams L, Proudman S, Wiese M. Adherence to combination DMARD therapy and treatment outcomes in rheumatoid arthritis: A longitudinal study of new and existing DMARD users. *Rheumatol Int*. 2017;37(6):897-904. [CrossRef]
13. Stolshek BS, Wade S, Mutebi A, De AP, Wade RL, Yeaw J. Two-year adherence and costs for biologic therapy for rheumatoid arthritis. *Am J Manag Care*. 2018;24(8 Spec No.):SP315-SP321.
14. Lu C, Wallace BI, Waljee AK, Fu W, Zhang Q, Liu Y. Comparative efficacy and safety of targeted DMARDs for active psoriatic arthritis during induction therapy: A systematic review and network meta-analysis. *Semin Arthritis Rheum*. 2019;49(3):381-388. [CrossRef]
15. Fries JF, Krishnan E. Equipoise, design bias, and randomized controlled trials: The elusive ethics of new drug development. *Arthritis Res Ther*. 2004;6(250):R250. [CrossRef]
16. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): A UK multicentre, open-label, randomised controlled trial. *Lancet*. 2015;386(10012):2489-2498. [CrossRef]