JAK inhibitors in combination with anti-TNF drugs on difficult-to-treat chronic polyarthritis: a case series

Sirs,

In clinical practice, there is a subset of patients with chronic polyarthritis who do not reach low disease activity or remission despite several cycles of conventional synthetic (cs), biological (b) and/or targeted-synthetic (ts) disease modifying anti-rheumatic drugs (DMARDs). Although criteria to define this group of patients exist for rheumatoid arthritis (RA), there are no clear definitions for other forms of arthritis (1, 2). To date, clinical guidelines towards the optimal treatment of these "difficult-to-treat" patients are lacking. Under this situation, a subset of clinically active patients with no or few comorbidities may benefit from the combination of advanced therapies.

We set out to describe our experience on the efficacy and safety of tsDMARD in combination with a bDMARD in a case series of three patients with difficult-to-treat forms of chronic polyarthritis in our centre between May 2020 and July 2023. Demographic, clinical and changes in laboratory data are shown in Table I.

Patient A is a 61-year-old female diagnosed with psoriatic arthritis (PsA), with axial and peripheral involvement. Bilateral hip replacement and bilateral knee synoviorthesis were present. Previous therapies are included in Table I. Eventually, upadacitinib 15 mg po was started and after 6 months of monotherapy, high disease activity persisted, so adalimumab 40 mg sc biweekly was added to the treatment.

Patient B is a 34-year-old patient diagnosed with oligoarticular juvenile idiopathic arthritis (JIA) with poor response to multiple DMARDs. Upadacitinib 15 mg po daily was started and one month later weekly etanercept 50 mg sc was added to the treatment regimen due to uncontrolled disease activity.

Patient C is a 35-year-old patient diagnosed with polyarticular JIA. Treatments before combination therapy were shown in Table I. Firstly, this patient received canakinumab-baricitinib combination therapy that was suspended due to primary failure. Secondly, combination therapy with upadacitinib 15 mg/day po and weekly etanercept 50 mg sc was initiated. This combination was temporarily held for right knee replacement.

Despite being pathogenically distinct forms of arthritis, in our case series all three difficult-to-treat patients showed reduction in disease activity through both composite and laboratory measures after combination therapy initiation (Table I).

Flare-ups of the disease occurred when combination therapy was temporarily stopped (Supplementary Fig. S1). Persistence of high disease activity 3 months after the last reintroduction of combination therapy led to its discontinuation in patient B.

Notably, glucocorticoids could be gradually tapered in all patients, and in 2/3 of them the daily prednisone dose could be reduced to ≤5 mg. No serious adverse events were reported in any of our patients.

The rationale for combining anticytokine agents is to simultaneously block different signaling pathways of the inflammatory response. We combined upadacitinib and anti-TNF agents to target the JAK-STAT and NF-κB pathways, respectively.

Evidence is scarce when it comes to combining biological agents and/or tsDMARDs in inflammatory arthritides. A meta-analysis including 6 studies evaluating b-DMARD combination therapy (none of them included tsDMARDs) in RA showed a modest risk of adverse events (AEs), with a median follow-up of 9.5 months (3).

Conversely, in a retrospective case series of nine patients with spondyloarthritis treated with anti-TNF agent plus IL-17, IL12/23R, IL23R or α4/β7-integrin antagonists major clinical improvement was reported (4). Median exposure was 14.8 months.

To our knowledge, only two case series have reported results on the combination of tofacitinib and bDMARDs in RA or PsA patients (5, 6). Partial or transient response

Table I. Summary of patient characteristics and treatment course.

	Patient A	Patient B	Patient C
Gender	Female	Female	Female
Age (years)	62	34	35
Diagnosis	PsA	JIA	JIA
Disease duration (years)	43	18	34
History of joint replacement surgery	Yes	No	Yes
Comorbidities	Dyslipidaemia	Obesity	Smoking
ANA	Negative	Positive	Negative
Anti-CCP	Negative	Negative	Negative
Rheumatoid factor	Negative	Negative	Negative
MEFV gene	Negative	Negative	Positive
HLA-B27	Positive	Negative	Negative
Glucocorticoid use	Yes	Yes	Yes
Previous DMARDs	MTX, SSZ, IFX, ADA, SCK, GOL, UST, TOF	MTX, SSZ, LEF, CYA, ADA, TCZ, ABT, ETN, RTX, CER, ANK, IFX, IXE, TOF	MTX, LEF, COL, CYA, IFX, ETN, ADA, TCZ, ANA, RTX, ABT, SARI, TOF, CAN
Combination therapy	UPA + ADA	UPA + ETN	(1) CAN + BAR (2) UPA + ETN
Combo follow-up period (weeks)	66	107	(1) 25 (2) 111
Initial CPR (mg/L)	98	33	18
Latest CPR (mg/L)	9	33	1
Initial ESR (mm/h)	101	35	46
Latest ESR (mm/h)	61	59	9
Initial activity score (DAS-28 or BASDAI*)	5.1*	6.1	7.3
Latest activity score (DAS-28 or BASDAI*)	2.0 *	5.31	2.38
Initial glucocorticoid dose (mg/day)	7.5	12.5	10
Latest glucocorticoid dose (mg/day)	5	15	3.75
Adverse events during combination therapy	UTI	Mild COVID-19 infection	Minor bone fracture Mild COVID-19 infection

(*) BASDAI for patient A.

ABT: abatacept; ADA: adalimumab; ANA: antinuclear antibodies; ANK: anakinra; BAR: baricitinib; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CAN: canakinumab; CCP: cyclic citrullinated peptide; CER: certolizumab; COL: colchicine; CRP: C-reactive protein; CYA: cyclosporine A; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; ETN: etanercept; GOL: golimumab; HAQ: Health Assessment Questionnaire; HLA: human leukocyte antigen; IFX: infliximab; IXE: ixekizumab; JIA: juvenile idiopathic arthritis; LEF: leflunomide; MTX: methotrexate; PsA: psoriatic arthritis; RA: rheumatoid arthritis; RTX: rituximab; SCK: secukinumab; SSZ: sulfasalazine; TCZ: tocilizumab; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; UTI: urinary tract infection.

with few SAEs was reported. Only one patient was treated with the combination of JAKi and anti-TNF (5).

Combination therapy with upadacitinib and anti-TNF agents in our case series proved effective in reducing disease activity in difficult-to-treat patients, for whom optimal therapeutic alternatives were lacking. No serious adverse events during the long follow-up were reported. Therefore, it might be a therapeutic option for selected patients.

S. Leal, *MD*
J. Ivorra-Cortés, *MD, PhD*
M. De La Rubia-Navarro, *MD*
C. Pávez-Perales, *MD*
C. Riesco-Bárcena, *MD*
J.A. Román-Ivorra, *MD, PhD*

Rheumatology Department,
Hospital Universitario y Politécnico La Fe,
Valencia, Spain.

Please address correspondence to:
José Ivorra Cortés
Rheumatology Department,
Hospital Universitario y Politécnico La Fe,
Avenida de Fernando Abril Martorell 106,
46026 Valencia, Spain.
E-mail: jivorra1@gmail.com

Competing interests: none declared.

References

1. NAGY G, ROODENRIJS NM, WELSING PM *et al.*: EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021; 80: 31-5. https://doi.org/10.1136/annrheumdis-2020-217344
2. NAGY G, ROODENRIJS NMT, WELSING PMJ *et al.*: EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2022; 81: 20-33. https://doi.org/10.1136/annrheumdis-2021-220973
3. BOLETO G, KANAGARATNAM L, DRAMÉ M, SALMON J-H: Safety of combination therapy with two bDMARDs in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2019; 49: 35-42. https://doi.org/10.1016/j.semarthrit.2018.12.003
4. VALERO C, BALDIVIESO JP, GONZALEZ-ALVARO I, TOMERO E, CASTAÑEDA S, GARCÍA-VICUÑA R: Effectiveness and safety of combined biological therapy in patients with refractory multidomain spondyloarthritis. *Ann Rheum Dis* 2022; 81: 899-901. https://doi.org/10.1136/annrheumdis-2021-221812
5. BARROSO NS, MILLER EZ, FURST DE: A case series on patients on tofacitinib in combination with a biologic. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis* 2018; 24: 349-51. https://doi.org/10.1097/rhu.0000000000000663
6. SHUREY M, YIP A, ZIOUZINA O, CHAN J, DUTZ JP: Combination therapy with tofacitinib and IL-12/23, IL-23, or IL-17A inhibition for the treatment of refractory psoriatic arthritis: a case series. *JCR J Clin Rheumatol* 2022; 28: e626. https://doi.org/10.1097/rhu.0000000000001767