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Title Page

Combination Therapy with JAK Inhibitors and TNF Inhibitors in Severe Refractory Rheumatoid Arthritis: A Monocentric Case Series

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Highlights:

- Multi-refractory rheumatoid arthritis remains a major therapeutic challenge, as a subset of patients fails multiple conventional and advanced therapies (b/tsDMARDs).
- We report a monocentric retrospective case series of six patients with severe, long-standing RA treated with a combination of a JAK inhibitor and a TNF inhibitor after multiple failure of targeted therapies.
- The safety profile appeared acceptable in this highly selected cohort, with no major infections, thromboembolic events, or cardiovascular complications observed during follow-up.
- Although not supporting routine use, JAKi–TNFi combination therapy may represent a rescue strategy for carefully selected patients with severe multi-refractory RA under strict monitoring.

Abstract

Background: A subset of patients with rheumatoid arthritis (RA) remains refractory despite sequential use of conventional synthetic and biological/targeted synthetic DMARDs (b/tsDMARDs). For these multi-refractory cases, therapeutic options are limited. Data on the concomitant use of Janus kinase inhibitors (JAKi) and tumor necrosis factor inhibitors (TNFi) are scarce.

Objectives: To describe our monocentric experience with combination therapy (CoT) using JAKi and TNFi in highly selected patients with severe, long-standing, multi-refractory RA, focusing on clinical response and safety.

Methods: We conducted a retrospective observational case series at a tertiary rheumatology center. RA adult patients who had failed multiple b/tsDMARDs and received concomitant JAKi and TNFi were included. Clinical, serological, and radiographic characteristics were collected. Disease activity (DAS28-CRP, CDAI, SDAI), patient-reported outcomes, glucocorticoid (GC) use, treatment persistence, and adverse events were assessed.

Results: Six patients with erosive, long-standing RA received CoT after a median disease duration of 192 months and at least five prior b/tsDMARD lines. Combinations included Infliximab, Etanercept or Adalimumab with Upadacitinib or Filgotinib. Four of six patients achieved remission or low disease activity, accompanied by progressive GC tapering and discontinuation in two cases. At 18- and 36-month follow-up (two patients), disease control was maintained without major infections, thromboembolic events, or cardiovascular complications.

Conclusions: In this small, highly selected cohort of severe multi-refractory RA, JAKi–TNFi combination therapy was associated with meaningful clinical improvement and an acceptable short- to mid-term safety profile. Although not supporting widespread use, our findings suggest that, under strict monitoring and individualized risk–benefit assessment, this strategy may represent a rescue option in exceptional cases. Larger prospective studies are needed to better define efficacy and safety.

Keywords

Rheumatoid Arthritis, Combination Therapy, Refractory Rheumatoid Arthritis, JAKi, TNFi

1. Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease characterized by synovitis involving multiple joints. In severe and chronic stages, RA can lead to joint destruction, deformity, disability and functional impairment (1). Recent advances in RA management allow good disease control in most patients, achieving remission or at least a low disease activity (LDA) and preventing chronic damage. Nowadays, the therapeutic

algorithm is based on the use of methotrexate (MTX) as the anchor drug with or without low-dose glucocorticoids (GCs), and the eventual association with biologic or targeted synthetic DMARDs (b/tsDMARDs) when disease control is not achieved (2). The large availability of b/tsDMARDs dramatically increased disease control in RA that is indeed reached by most patients. However, some of them still exhibit active disease despite advanced therapy. Those patients, referred to as “multi-refractory RA”, still represent a challenge for clinicians: they show transversal resistance to multiple biologics with different mechanisms of action (MoA) and fail to achieve a state of remission, being exposed to high disease activity over time (3). As a result, they develop chronic damage, disability and are exposed to high doses of GCs in the extreme effort to relieve pain and to control disease activity (4). For these patients, innovative therapeutic strategies are lacking and to date no clear strategy besides cycling and switching between different MoA is available.

Although EULAR and ACR recommendations do not support the combination of multiple b/tsDMARDs (5), the need for solutions in severe refractory patients led the investigation to treatment strategies including biological combination therapy, with contrasting results (6). Although the rationale for combining biologics with different MoA is theoretically attractive, benefits did not always outweigh the risks.

To date, very few data are available on the combination of JAKi and TNFi in RA and no assumptions can be made.

This study aims to share our experience with combination therapy (CoT) of JAKi and TNFi with a special focus on patient selection and safety.

2. Methods

2.1 Study Design and patients selection

This is a monocentric, observational retrospective case series study conducted at a tertiary referral rheumatology center (Cliniques Universitaires Saint-Luc, UCLouvain, Bruxelles, Belgium). The study aimed to describe the clinical characteristics, treatment course, safety and outcomes of patients with RA treated with a combination of a JAKi and TNFi.

Adult patients (≥18 years) with a diagnosis of RA according to the 2010 ACR/EULAR classification criteria (7) were eligible for inclusion. The decision to start combination therapy was taken after the demonstration of multi-refractory disease to multiple mechanisms of action. Specifically, patients who were seropositive for FR and ACPA had failed at least one TNF-inhibitor, anti-IL-6R, JAK inhibitor and B-/T-cell-targeted therapy (rituximab and/or

abatacept), whereas for seronegative patients, combination therapy was prescribed after at least a TNFi, anti-IL-6R and a JAKi were failed. These patients received concomitant therapy with a JAKi and a TNFi for any duration within the study period. The decision to initiate combination therapy was shared by the treating physician and the RA patient based on clinical judgment, including disease activity, prior treatment failures, and individual patient characteristics.

2.2 Data Collection

Clinical and demographic data were collected from electronic medical records. Patients underwent a baseline assessment and subsequent follow-up visits according to routine clinical practice. The following variables were recorded: age, sex, smoke status, body mass index (BMI), disease duration, serological status [rheumatoid factor (RF) and anti–citrullinated protein antibodies], radiographic damage (bone erosions) on hands and feet X-rays, prior and concomitant DMARDs, presence of extra-articular manifestations, vaccines received and comorbidities.

Disease activity was assessed using standard composite indices, including the Disease Activity Score in 28 joints (DAS28), Clinical disease activity score (CDAI) and (SDAI). Laboratory parameters (e.g., C-reactive protein) were collected at baseline and during follow-up. Patient-reported outcomes (PROs) were collected using visual analogue scales for patient global assessment (VASp) and pain (VASpain), while physician global assessment was also recorded (VASm). Functional status was evaluated using the Health Assessment Questionnaire (HAQ).

Concomitant treatments were documented at each visit, including the use of csDMARDs, oral GC—reported as prednisone-equivalent daily doses—and non-steroidal anti-inflammatory drugs (NSAIDs).

JAKi and TNFi were administered according to approved dosing regimens. Treatment duration, dose adjustments, and discontinuation reasons were documented.

3. Results

We included six patients with a median age of 39.5 years (IQR20). Patients received a combination therapy after a median of 192 months (IQR 120) from RA diagnosis and at least five previous treatment lines with b/tsDMARDs. Two patients presented extra-articular

manifestations with non-specific interstitial pneumonia (NSIP). All of them had erosive disease. Specifics regarding demographic and disease-related features are reported in Table 1.

All patients received a combination of TNFi and JAKi: three patients were treated with Infliximab and Upadacitinib, one with Etanercept and Upadacitinib, one with Etanercept and Filgotinib and the last with adalimumab and Filgotinib.

Five patients were younger than 55 years, with a severe aggressive disease and few or no comorbidities. Only one patient differed from this profile being 66 years old and with 3 cardiovascular risk factors (patient n°3). In this patient, combination-therapy was introduced because of progressive active joint disease with significant extra-articular manifestations (NSIP) and high-dose GC exposure. None of them was an active smoker. As evident in table 1 and Figure 1, all these patients failed multiple treatment lines with different MoA because of a real refractory disease after a long disease duration. Except for patient n°3, who was diagnosed with latent tuberculosis (TBC) and treated before the introduction of the first biological therapy, no personal history of major infection, including herpes zoster, was recorded.

Patients were followed monthly during the first three months and every three months thereafter, or earlier if needed.

Following the disease activity after the CoT initiation, we observed a slow progressive decrease in four out of six patients (Figure 1B) reaching remission or LDA. Regarding the other two, one (patient n°2) discontinued CoT early due to a major allergic reaction to Infliximab, while patient n°3 never achieved adequate disease control and CoT was discontinued after 6 months. Patient n°1 discontinued the CoT after three months and kept monotherapy because of fast remission induction. Notably, in four patients, combination therapy allowed for a gradual reduction in glucocorticoids, leading to complete discontinuation in two patients.

At the present time, an open follow-up is available for two out of six patients (for patients n °5 and n°6, respectively, with follow-up durations of 18 and 36 months): after the introduction of CoT, they reached and maintained low disease activity (LDA) or remission. None of them developed major cardiovascular events or infections. No side effects were reported with CoT

except allergic reactions to infliximab. According to comorbidities, age and personal tailored risk, vaccination against influenza and/or pneumonia was recommended.

4. Discussion

In this case-series we present our monocentric experience with combination therapy (JAKi and TNFi) in RA. We show how in young, selected and severe refractory patients, CoT may be an innovative and effective option to achieve a good disease control.

RA is a chronic disease and despite the large availability of different b/tsDMARDs a not negligible percentage of patients fail to achieve a persistent good disease control. These patients, referred to as “refractory” or “multi-resistant” RA, represent a challenge for clinicians and different treatment strategies failed to demonstrate superiority (8).

Combination therapy may therefore be an option. To date, data are scarce and the general feeling is that combining JAKi and bDMARDs is too risky, especially for serious infections, malignancies and major adverse cardiovascular events (MAVE) (9). In our cohort, even though small, we did not experience any serious side effect.

To the best of our knowledge, only one recent paper explored the possibility to combine these treatments in RA (10): twenty-eight patients received tofacitinib 5 mg twice daily in combination with bDMARDs (22 TNFi, 6 anti-IL6R) when disease remission was not achieved with biologics alone after three months of first line therapy. This strategy was superior to bDMARDs alone in terms of decrease of DAS28-ESR at week 24. Except for 4 herpes zoster infections (14.2%), no other major infections or other adverse events were recorded.

However, our study has some differences with the reported study. In our small cohort, treatment strategy was different: none of them received tofacitinib but rather three Filgotinib and three upadacitinib, all in combination with TNFi. The median age was different as well, patients being older in the study from Chang and colleagues.

However, the main difference lies in patients selection: they evaluated JAK inhibitors (JAKi) combined with bDMARDs as a second-line therapy when the first bDMARD proved

ineffective, whereas in our study JAKi + TNFi were used as a last-line treatment in patients with severe, refractory disease. Despite these differences, the results are comparable: combination therapy (CoT) appears effective and associated with an acceptable rate of adverse events, mainly infections.

Although there are no other descriptions of patients treated with combinations of JAKIs and TNFIs, since the early 2000s there have been various attempts to combine different biological drugs: TNFi plus anti-IL1 and TNFi plus abatacept did not show superiority of CoT over classical strategies with some safety concerns (11,12). However, in these studies, drug combination was started after the failure of first line MTX, a choice that nowadays would not be supported given the large availability of different JAKi and bDMARDs.
When correctly placed, CoT may represent a possibility. In patients with longstanding refractory RA, TNFi or abatacept combined with Rituximab (RTX) could offer a therapeutic advantage with an acceptable risk of adverse events (13,14).

Beside RA, CoT is an appealing approach in other diseases such as Spondyloarthritis (SpA) and psoriatic arthritis (PsA) where heterogeneous manifestations (i.e uveitis, psoriasis, inflammatory bowel disease) overlap and a single MoA may not globally control all the possible manifestations. In this scenario, a dual therapy, blocking different cytokines, emerged as a safe possibility. A recent meta-analysis resumed these findings showing how for PsA, ax-SpA and RA the most common combinations were TNFi+IL-23i and JAKi combined with bDMARDs without raising significant safety issues (15,16).

The novelty of our approach lies on the combination of JAKi and TNFi. The rationale for combining a JAK inhibitor with a TNF inhibitor lies in their complementary mechanisms of action within the inflammatory cascade. JAK inhibitors interfere with intracellular JAK-STAT signaling downstream of multiple cytokine receptors, modulating a broader network of pro-inflammatory pathways that are complementary to those modulated by TNFi.

Unlike dual biologic therapy—where two bDMARDs may target parallel or partially overlapping extracellular mediators—JAK inhibition acts at a shared intracellular signaling hub, potentially reducing cytokine redundancy and compensatory pathway activation. This mechanistic complementarity may theoretically provide a more integrated suppression of

immune activation compared with combining two biologics that each block a single cytokine axis.

In this context, our findings should not be interpreted as an encouragement for widespread use of combination targeted therapies, but rather as a proof of concept suggesting that patients with very severe and refractory RA could be eligible under specific circumstances and strict monitoring, and this approach may represent a reasonable rescue strategy. These considerations provide the framework for the following conclusions.

In conclusion, this monocentric case series suggests that the combination of JAK inhibitors and TNFi may represent a feasible therapeutic option in highly selected patients with severe, long-standing, and multi-refractory RA. In our experience, combination therapy was associated with meaningful clinical improvement in most patients, with an acceptable safety profile over the observed follow-up period.

Although current international guidelines discourage the concomitant use of multiple targeted therapies because of safety concerns, our findings indicate that, in carefully selected young patients with limited comorbidities and under strict clinical monitoring, this strategy may offer a valuable alternative when all conventional options have failed.

Nevertheless, the small sample size, the retrospective design, and the monocentric nature of this study limit the generalizability of our results.

Until more robust evidence becomes available, this therapeutic approach should be considered only in exceptional cases, within experienced centers, and after a thorough individualized risk–benefit assessment.

Author contributions

FN: Data curation, Formal analysis, Investigation, Visualization, Writing
CVM: Investigation, Writing – review & editing.
SD: Investigation, Writing
PD: Conceptualization, Writing – Review:
All authors contributed to the interpretation of data, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript.

Consent to participate

Oral informed consent was obtained from all patients prior to participation.

Declaration of conflicting interest

Authors have no conflict of interest to declare.

Data availability

Data are available under reasonable request.

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Figure 1.

Clinical response and treatment history in patients treated with combination therapy. Each line represents an individual patient.
(A) Trend of disease activity over time, assessed by DAS28-CRP, from baseline to 24 months after initiation of combination therapy.
(B) Trend of patient-reported pain, assessed by visual analogue scale (VAS pain), during follow-up.
(C) Sankey diagram illustrating previous and subsequent treatment lines and switches between different b/tsDMARDs in the study population. Each flow represents a therapeutic transition.

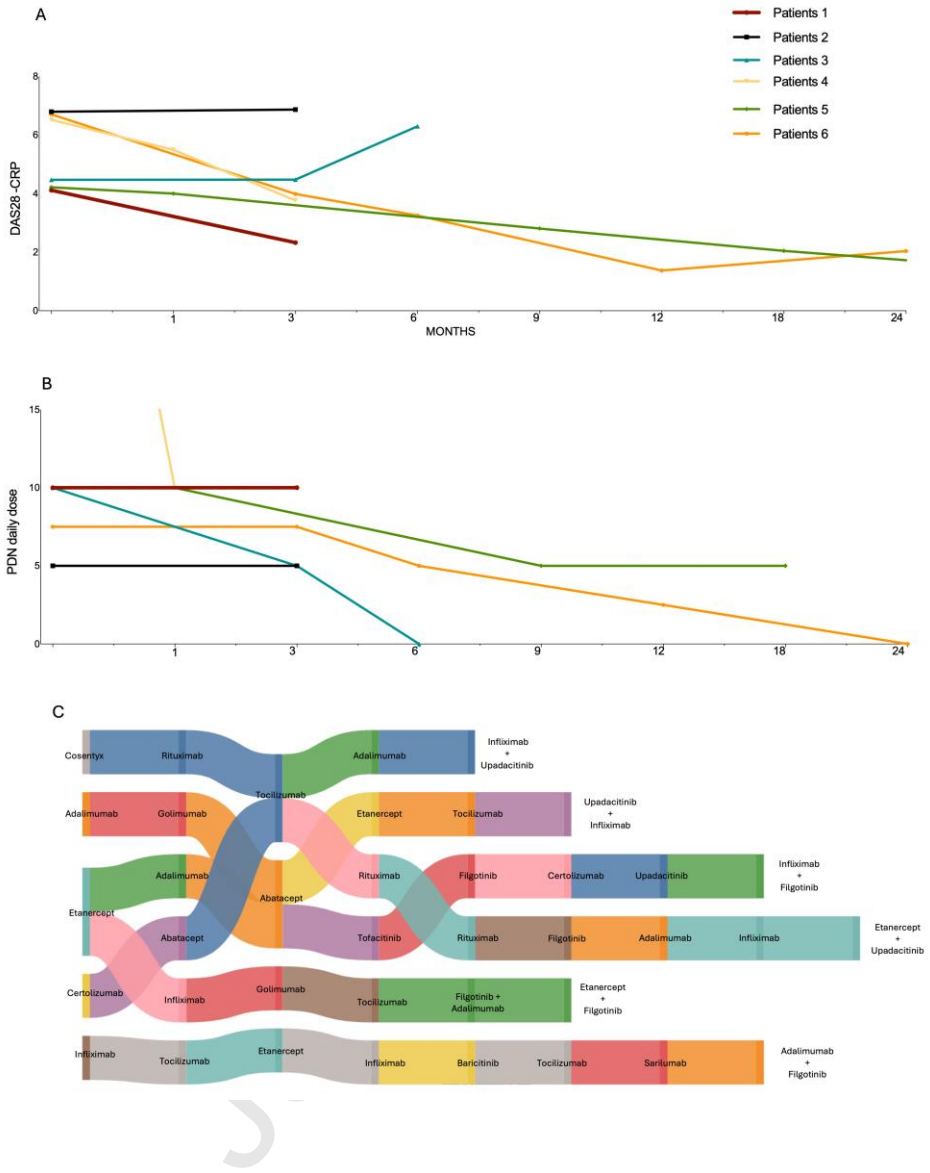

Table 1. Baseline demographic, clinical, and treatment characteristics of patients treated with combination therapy.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Female	Male	Female	Female	Male	Female
BMI	25.4	29.9	30	25.4	21	19.7
Smoke	No	No	Ex	No	No	No
ACPA	No	Yes	Yes	Yes	No	No
RF	Yes	Yes	Yes	No	No	0
Erosions	Yes	Yes	Yes	Yes	Yes	Yes
Age at combination	36	55	66	43	35	34
Extra articular manifestation	-	NSIP	NSIP	-	-	-
Time to combination (months)	162	348	282	156	216	168
Combination therapy exposure (months)	3	3	6	3	18	36
Ongoing combination therapy	No	No	No	No	Yes	Yes
Reason for interruption	Fast Response	Allergic Reaction	Inefficacy	-	-	-
Comorbidities	Arterial Hypertension	Metabolic Syndrome, Osteoporosis	Diabetes, Obesity, Hypercholesterolemia, Latent TBC treated in 2007	-	-	-
csDMARDs	Hydroxychloroquine	Methotrexate	-	Methotrexate, Leflunomide	-	Methotrexate

Table1.

Legend. The table summarizes sex, body mass index, serological status, radiographic damage, extra-articular manifestations, disease duration, exposure to combination therapy, vaccination status, smoking habits, comorbidities, and reasons for treatment interruption in the six included patients. Abbreviations: ACPA, anti–citrullinated protein antibodies; RF, rheumatoid factor; BMI, body mass index; NSIP, non-specific interstitial pneumonia; TBC, tuberculosis; DMARDs, disease-modifying antirheumatic drugs