Case Series

Newer immunomodulators in rheumatoid arthritis: A cautionary tale for cardiologists

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Background

Cardiotoxicity can result in serious complications, including heart failure, cardiomyopathy, arrhythmias, myocardial infarction (heart attack), myocarditis (inflammation of the heart muscle), and sudden death Two cases of suspected drug-induced cardiac events are presented, highlighting the possible real-world implications of these risks.

Keywords: Ankylosing spondylosis; Tofacitinib; Rheumatoid arthritis; Immunosuppressive medications

1. Case Presentation

1.1 Case 1

58-year-old male Mr. AK, k/c/o Type 2 Diabetes Mellitus of 3 years' duration, systemic Hypertension, diagnosed to have Ankylosing spondylosis at 30 years of age on immunomodulators. He was referred to us for preoperative fitness for cholecystectomy and inguinal hernia surgery. He was symptomatic for Ankylosing spondylitis and denied any cardiac symptoms at the time of evaluation. Clinical examination was Normal. ECG was within normal limits. ECHO revealed Dilated Left Ventricle, Global LV hypokinesia with and moderate LV systolic dysfunction, LVEF –35%, Trivial MR and TR, Normal RV function (figure-1). Previous ECHO was within normal limits 2 years ago. Coronary angiogram showed Minimal Coronary artery disease (Diagonal ostium had 30% stenosis and Mid RCA had 40% tubular stenosis). Retrospectively he was found to be treated with Tab. Tofacitinib 5mg BD, Tab. Etoricoxib for past 2 years for ankylosing spondylitis. The case was discussed with rheumatologist and was suggested to stop the drug Tofacitinib and it was replaced with monthly secukinumab injections (IL-17 antagonist). He was discharged with statins, Beta blockers and ACE inhibitor therapy X.

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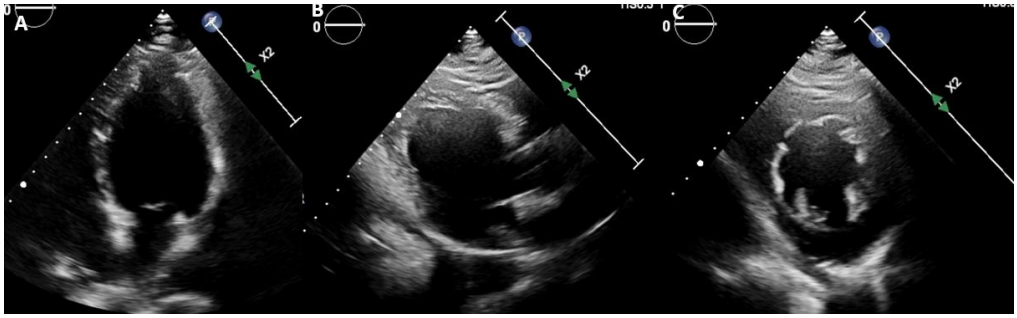

Figure 1 (A): Apical four chamber view

Figure 1 (B): PLAX view

Figure 1 (C): Short axis view2

1.2. Case 2

51-year-old male Mr.VA, k/c/o Rheumatoid arthritis and no other comorbidities, presented to us with history of chest pain, associated with breathlessness of 4 hours' duration. He was diagnosed to have Acute Coronary Syndrome /Inferior Wall Myocardial Infarction. ECHO revealed regional wall motion abnormalities in LCX territory with Mild LV systolic dysfunction. STEMI team was activated and coronary angiogram was done which showed Double Vessel disease of Major OM and RCA (figure-2). Primary PCI to Major OM was done followed by staged PCI to RCA 48 hours later (figure-3). On detailed review, he was found to be on Tab. Tofacitinib 5mg BD, Tab. Methotrexate 15mg weekly, Tab. Folic acid for past 6 months. The case was discussed with Rheumatologist and the drug Tofacitinib was stopped.

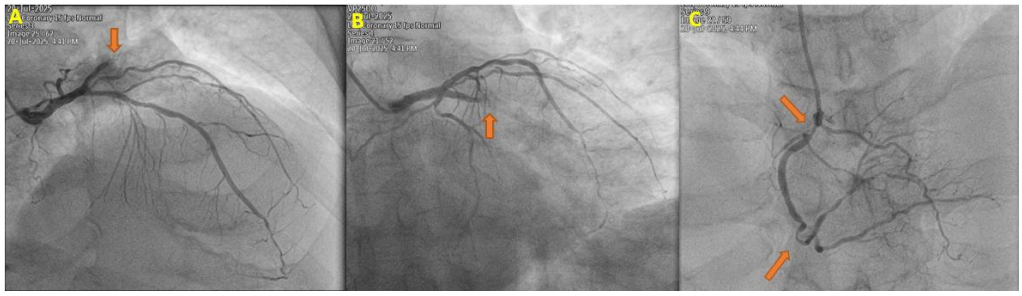

Figure 2 (A, B): Fluoroscopic images reveals Major OM-Total occlusion

Figure 2 (C): Fluoroscopic images reveals Proximal RCA-critical stenosis, RPLB-diffused disease

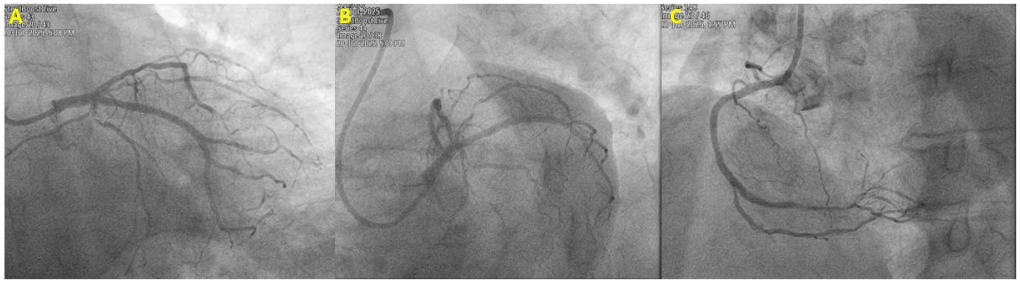

Figure 3 (A, B): Fluoroscopic images reveals TIMI –III flow after PCI to MAJOR OM using 1 Drug Eluting Stent.

Figure 3 (C): Fluoroscopic images reveals TIMI III flow after PCI to RCA using 1 DES, to R-PLB using 1 Drug Eluting Balloon.

2. Summary

Janus kinase (JAK) inhibitors are immunosuppressive medications that target the JAK-STAT signaling pathway, which is involved in pro-inflammatory processes. Several JAK inhibitors are currently approved for the treatment of rheumatoid arthritis (RA), and each has a distinct selectivity for the different JAK family members (JAK1, JAK2, JAK3, and tyrosine kinase 2). Due to their distinct molecular activity, potential differences in their efficacy and safety profiles are the subject of active research.

Tofacitinib was the first JAK inhibitor product to be approved by the Food and Drug Administration (FDA) for the treatment of RA. The clinical development program of tofacitinib has raised concerns about a potential increased risk of cardiovascular events prompting the FDA to require a randomized, safety end-point, clinical trial to assess the risk of treatment-related MACE. The post marketing ORAL Surveillance clinical trial found a higher incidence of MACE and venous thromboembolism (VTE) following tofacitinib treatment compared to tumor necrosis factor-alpha (TNF) inhibitors. These findings led the FDA to issue a safety warning regarding blood clots and heart-related events for tofacitinib and two other JAK inhibitor medications, Upadacitinib and baricitinib, while acknowledging that these agents have not been adequately evaluated in large clinical trials.

3. Literature Review

1. Large-scale studies found an increased incidence of non-fatal MI and other MACE in patients treated with tofacitinib, particularly at higher doses or in those with cardiovascular risk factors (HR for MACE up to 2.2 vs. TNF inhibitors).

2. The ORAL Surveillance trial and similar real-world evidence point to a non-statistically significant but numerically higher risk of cardiovascular events and thrombotic complications.

3. Tofacitinib increases MACE risk: Recent studies show patients with rheumatoid arthritis, especially those over 50 or with existing atherosclerotic cardiovascular disease (ASCVD), have a higher risk of major adverse cardiovascular events (MACE)—like heart attack or sudden cardiac death—when treated with tofacitinib compared to TNF inhibitors, with a hazard ratio up to 1.98 in higher-risk groups.

4. Patient selection matters: Patients without prior ASCVD but with risk factors didn't show a large difference from TNF inhibitors at standard dosing; however, those with a history of ASCVD or a high 10-year ASCVD risk have the highest risk for new cardiac events.

5. Dose-dependent risk: The risk appears most pronounced at higher doses (10 mg twice daily), which led to FDA black box warnings and recommendations to use the lowest effective dose.

6. Venous thromboembolism (VTE) caution: Tofacitinib use, especially at higher doses, is linked to higher rates of VTE, notably pulmonary embolism, relative to TNF inhibitors

7. Most of the events occurred in the first year after treatment initiation. Among JAK inhibitor agents, Upadacitinib and baricitinib had higher reporting of VTE, stroke, and IHD than tofacitinib.

8. International drug safety authorities now recommend extra caution or alternate therapy in patients over 65, smokers, or those with established CVD.

4. Discussion

Here we present two cases with background two different autoimmune diseases on same immunomodulatory drug Tab. Tofacitinib (JAK kinase inhibitor) of different duration with varied presentations. Case 1 presented to us with asymptomatic LV dysfunction with non-obstructive coronaries. He was on Tofacitinib 5mg BD for 2 years. Case 2 presented with Acute coronary syndrome with Multivessel disease and underwent Primary PCI. He was on the same drug for 6 months (5mg BD). Literature review clearly shows increased cardiac events and thrombotic complications associated with the drug and a black box warning for the same. This is a wakeup call for cardiologists, as we are not aware of such drug and its associated cardiac events. We need to be more vigilant in getting the drug history especially in patients with autoimmune diseases. All patients on such drugs should be educated regarding the same and made aware of potential risks involved with these drugs and should be put under surveillance for LV dysfunction with or without symptoms.

JAK inhibitors are preferred by rheumatologists because of its faster onset of action (1-2 weeks) compared to cDAMARDs which takes 8-12 weeks, Oral convenience, ease of use as Monotherapy and broader efficacy across disease domains. Literature says, the risk is increased when the drug is used in patients over 50 years, established ASCVD or high ASCVD scores and higher doses of the drug. In our cases, both the patients are over 50 years with high ASCVD scores. So it is better to avoid this group of drugs in these patient subsets. In case 1, Tofacitinib was replaced with IL-17A antagonist, Secukinumab, a fully monoclonal antibody. FDA has approved its used in psoriasis, psoriatic arthritis and Ankylosis spondylitis and it lacks the cardiovascular risk signals seen with JAK kinase inhibitors. Other safer alternatives would be Biological DMARDs such as TNF inhibitors (Adalimumab, Etanercept), synthetic DMARDs such as Methotrexate and triple therapy combining it with sulfasalazine and hydroxychloroquine. More selective JAK inhibitors like Filgotinib, a selective JAK-1 inhibitor, approved in EU, seems to have better safety profile.

5. Conclusion

Emerging evidence supports a cautious approach to tofacitinib and its related drugs, especially in higher-risk individuals. Individual patient risk factors for cardiovascular disease should be considered prior to initiating therapy, and clinicians should monitor closely for cardiac events.

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