A rare case of symptomatic creatine kinase elevation in a patient with rheumatoid arthritis treated with baricitinib

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SUMMARY

The safety profile of baricitinib (BARI), a Janus kinase inhibitor broadly used for the treatment of rheumatoid arthritis (RA), includes asymptomatic laboratory abnormalities, such as an increase in creatine kinase (CK). Data from randomized controlled trials suggest that concomitant myalgia is rare in RA and does not lead to drug discontinuation.

We describe the case of a 68-year-old Caucasian female with longstanding, multi-failure RA who started BARI and achieved disease remission. However, she developed a symptomatic CK increase, as well as a parallel increase in total cholesterol, low-density lipoprotein, and triglycerides.

Dechallenge-rechallenge demonstrated a plausible relationship between the clinical/laboratory abnormalities and BARI. In fact, when the drug was withdrawn, CK returned to normal and myalgia disappeared, whereas symptoms returned and CK levels increased when BARI was restarted.

BARI may be rarely associated with symptomatic CK elevation, and this may pose clinical challenges, particularly for patients with multi-failure RA who achieved good disease control with BARI but required drug discontinuation due to intolerance.

Key words: *Case report, rheumatoid arthritis, baricitinib, creatine kinase, myalgia.*

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INTRODUCTION

Baricitinib (BARI) is a Janus kinase inhibitor (JAKi) broadly used for the treatment of rheumatoid arthritis (RA). Its safety profile encompasses various adverse events, such as an increased risk of infections, with herpes zoster being the most recognized opportunistic infection associated with JAKis (1). Asymptomatic laboratory abnormalities, including an increase in low- and high-density lipoproteins (LDL and HDL) and creatine kinase (CK), have also been described. Herein, we report a rare case of symptomatic CK increase after BARI treatment in a patient with RA.

CASE REPORT

A 68-year-old Caucasian woman was diagnosed with seronegative RA in 1992 and had been treated with hydroxychloroquine, sulfasalazine, methotrexate, adalimumab, and infliximab, which were discontinued due to inadequate response. She also received abatacept and etanercept, which were promptly discontinued due to allergic reactions and drug intolerance, respectively. She had no history of cardiovascular events despite being obese [body mass index (BMI) 31.2].

At the first referral to our institution in November 2021, we performed a comprehensive clinical and laboratory assessment, including retesting for rheumatoid factor and anti-cyclic citrullinated antibodies that resulted negative and testing for anti-nuclear antibodies that also resulted negative. Extra-articular manifestations of RA were also ruled out. Owing to active disease despite treatment with leflunomide (20 mg every other day) and glucocorticoids (GC) (2 mg/day) [disease activity score on 28 joints calculated using C reactive protein

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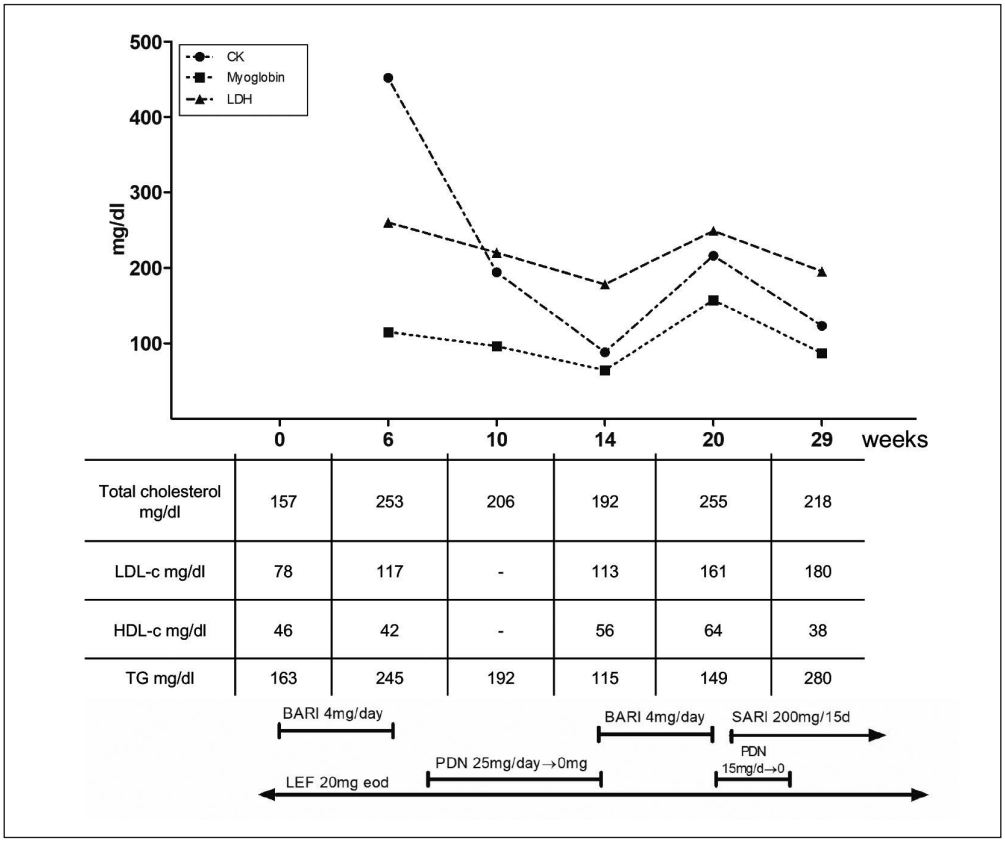
(DAS28-CRP) =5.42; clinical disease activity index (CDAI)=33], we deemed it appropriate to start BARI at 4 mg/day on top of leflunomide with a rapid GC tapering, and within 6 weeks we observed a prompt clinical and serological response (DAS28-CRP=1.96; CDAI=6.5). However, while acknowledging a marked improvement in articular symptoms, the patient complained about new-onset diffuse myalgia appearing about 2 weeks after starting BARI. We performed additional blood exams and observed elevated CK and myoglobin levels with normal liver function tests (Figure 1). The patient declined to perform electromyography. A parallel increase in total HDL and LDL cholesterol, as well as triglycerides (TG), was also observed. Therefore, we decided to stop BARI and refrained from adding a lipid-lowering agent (*e.g.*, statins) due to the coexisting myalgia. When reassessing the clinical and serological picture 4 weeks later, a consistent drop in CK values was observed, along with a reduction in TG, HDL, LDL, and total cholesterol. The patient reported that myalgia disappeared about a week after stopping BARI. We then reintroduced BARI 4 mg/day. We did not consider a lower dose due to the patient's BMI. Six weeks later, CK, myoglobin, TG, total, LDL, and HDL cholesterol were again above the upper limit of normal (ULN), and the patient also reported a recurrence of diffuse myalgia (Figure 1). Therefore, a cause-effect relationship between the drug and the above-mentioned abnormalities was plausible.

BARI was withdrawn, and the abnormal exams quickly returned within the normal



Total cholesterol mg/dl	157	253	206	192	255	218
LDL-c mg/dl	78	117	-	113	161	180
HDL-c mg/dl	46	42	-	56	64	38
TG mg/dl	163	245	192	115	149	280

Figure 1 - Timeline showing the results of laboratory tests from symptom onset to last follow-up. CK, creatine kinase; LDH, low-density lipoproteins; HDL, high-density lipoproteins; TG, triglycerides; BARI, baricitinib; LEF, leflunomide; PDN, prednisolone; SARI, serotonin antagonist and reuptake inhibitor.

limits, whereas the myalgia disappeared. Taking into account the previous therapeutic approaches, disease activity, BMI, and patient preferences, she was treated with sarilumab 200 mg/15 days (2). Eight weeks later, DAS28 remission was achieved (DAS28-CRP=2.08 CDAI=9), whereas CK, LDH, and myoglobin were reduced and myalgia had disappeared. Nonetheless, we noted a change in the lipid profile that could possibly be related to GC bridging therapy but also to sarilumab. However, we could rule out the latter since, once GC therapy was discontinued, the lipid profile returned to normal. Written informed consent was obtained from the patient.

DISCUSSION

To the best of our knowledge, this is the third reported case of BARI-induced symptomatic CK elevation in the RA post-marketing literature (3). It is interesting to note that the two previously described cases share similarities with ours. First, both patients had seronegative RA, and the myalgia occurred within a timeframe from the initiation of BARI therapy comparable to that of our case (7 days in the first case and 10 days in the second). In addition, in both cases, myalgia improved after about 7 and 14 days from the discontinuation of BARI. Concerning serological data, our patient was not tested for antibodies against other citrullinated antigens or proteins that underwent different post-translational modifications (*e.g.*, carbamylated proteins). However, since all three cases were seronegative for rheumatoid factor and anti-cyclic citrullinated peptide, the question remains about the possible presence of other autoantibodies and their role in the development of this adverse event.

Pooled safety data from 9 phase III/II/Ib randomized controlled trials (RCTs) and one completed long-term extension trial (14 744 patient-years of exposure) of BARI in RA reported asymptomatic CK elevation >5× ULN in 3.9% of patients (4). Likewise, a pooled analysis of 8 RCTs evaluating BARI in atopic dermatitis revealed that asymptomatic CK increase to at least grade 1 (>ULN to 2.5× ULN) was the most commonly detected laboratory change (23.8% of patients receiving a daily dose of 4 mg groups *versus* 10.3% of patients in the placebo group) (5, 6). Of interest, the authors reported that only a very small subgroup of patients, 32 out of the 2636 (1.2%) treated patients, exhibited symptoms of myalgia, notably without rhabdomyolysis (6). Interestingly, no RCT has reported any patient withdrawing BARI due to myalgia (4, 6).

Assuming therefore that a possible cause was not BARI per se but rather the combination of BARI and leflunomide, we investigated the literature and found that the only available data on adverse effects described in patients treated with this therapeutic combination are infections, modest thrombocytosis, and hemorrhagic events (7).

A proposed mechanism underlying CK elevation in RA patients treated with BARI is the inhibition of myoblast differentiation by cytokines such as oncostatin M, which in turn leads to decreased CK expression. Hence, blocking these cytokines, like oncostatin M, with JAKis such as BARI has been shown to restore muscle differentiation and thereby increase CK expression (6). Therefore, it can be inferred that the use of BARI can increase CK levels simply by restoring physiological muscle differentiation, and therefore the cause of associated myalgia remains unclear (8). Interestingly, BARI has recently been successfully used in the treatment of dermatomyositis, yielding positive results on both the cutaneous and the muscular manifestations (9-11). The rationale for this therapeutic application relates to the effects of JAKis on the type I interferon pathway (12). It is therefore intriguing to observe that the same molecule could be therapeutic or detrimental to muscle homeostasis.

The concomitant use of other drugs known to increase CK levels adds a layer of complexity to this matter. In fact, since BARI can increase cholesterol levels (4), new-onset muscle pain may be attributed to statins, which are sometimes necessary. This was not the case in our patient, but an iatrogenic cause (other than BARI) of the CK increase should always be ruled out.

CONCLUSIONS

In conclusion, our case highlights that clinicians should be alert about BARI-induced symptomatic CK elevation since it may lead to drug discontinuation despite being rare. This may pose clinical challenges, particularly for patients with multi-failure RA who achieved good disease control with JAKis (8).

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare no potential conflict of interest.

Ethics approval and consent to participate
Not applicable.

Informed consent
Written informed consent was obtained from the patient.

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Availability of data and materials
Data available from the corresponding author upon request.

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