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LETTER TO THE EDITOR

Novel use of interleukin-1 antagonists in male familial Mediterranean fever patients with infertility: Case series

Bugra Egeli[1], Kerem Parlar[2], Basak Filiz[2], Ibrahim Durucan[2], Serdal Ugurlu[2]

[1]*Department of Pediatrics, Children's Hospital of Los Angeles, University of Southern California, Los Angeles, California, USA*
[2]*Department of Internal Medicine, Division of Rheumatology, İstanbul University Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Istanbul, Türkiye*

Familial Mediterranean fever (FMF) is primarily treated with colchicine. For colchicine-resistant cases, interleukin (IL)-1 antagonists, such as anakinra and canakinumab, are used.[1] Male infertility, a rare FMF complication, is often attributed to long-term colchicine use,[2] although local testicular inflammation has also been suggested as a cause.[3] In patients with azoospermia or oligospermia, anti-IL-1 agents, such as anakinra or canakinumab, can replace colchicine.[4] Herein, we reported two male FMF patients with transient infertility who successfully conceived healthy embryos via *in vitro* fertilization (IVF) after switching from colchicine to anti-IL-1 agents.

A 38-year-old male patient with FMF (homozygous M694V mutation) on 2 mg daily colchicine for six years presented in January 2022, unable to conceive since 2007. The patient and his wife had attempted IVF five times. The patient ceased colchicine during the last three IVF attempts. A spermiogram showed normal viscosity, pH 7.2 (normal: 7.2-7.8), 3 mL volume (normal >1.5 mL), 25 million/mL concentration, 75 million total number (normal >39 million), 23% total motility (normal >32%), 0% Grade A rapid progressive motility, 15% Grade B slow progressive motility, 8% Grade C nonprogressive motility, and 77% Grade D immotility. The patient was switched to anakinra 100 mg daily at the end of January. In June 2022, they successfully obtained two genetically normal embryos suitable for transfer. In April 2022, a spermiogram showed pH 7.2, 4 mL volume, 39 million/mL concentration, 156 million total number, 45% total motility, 0% Grade A rapid progressive motility, 17% Grade B slow progressive motility, 28% Grade C nonprogressive motility, and 55% Grade D immotility.

A 33-year-old male with FMF and heterozygous M694V mutation, treated with colchicine for 14 years, presented with diarrhea. Due to gastrointestinal side effects of colchicine, anakinra was initiated. Concurrently, he was diagnosed with azoospermia during a urology evaluation for infertility. Although anakinra reduced attack frequency, it was discontinued at the IVF specialist's request. After an initial failed IVF attempt, colchicine was stopped and canakinumab was prescribed. Three subsequent IVF attempts failed due to poor embryo quality, but sperm quality gradually improved with canakinumab. Total motility increased from 35 to 60% after anti-IL-1 agent use. Ultimately, the couple had a child on the fifth IVF attempt, marking their first successful conception.

The evidence of healthy embryos in both cases is significant given the timeline of switching from colchicine to anti-IL-1, pointing

Correspondence: Serdal Ugurlu, MD.
E-mail: serdalugurlu@gmail.com

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towards the reversibility of the problem related to colchicine side effects or local inflammation. Both patients successfully had children via IVF after switching to anti-IL-1 agents. One patient (case 1) experienced increased sperm volume, concentration, total number, and motility, while the other (case 2) saw improved sperm motility. Colchicine resistance is suggested to predict infertility in FMF patients,[5] and better disease control may alleviate local inflammation associated with inadequate colchicine response.

In conclusion, infertility may be reversible in patients experiencing inflammation or receiving prophylactic colchicine. Anti-IL-1 agents could become the preferred treatment for male FMF patients with reproductive issues.

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