The influence of safety warnings on the prescribing of JAK inhibitors

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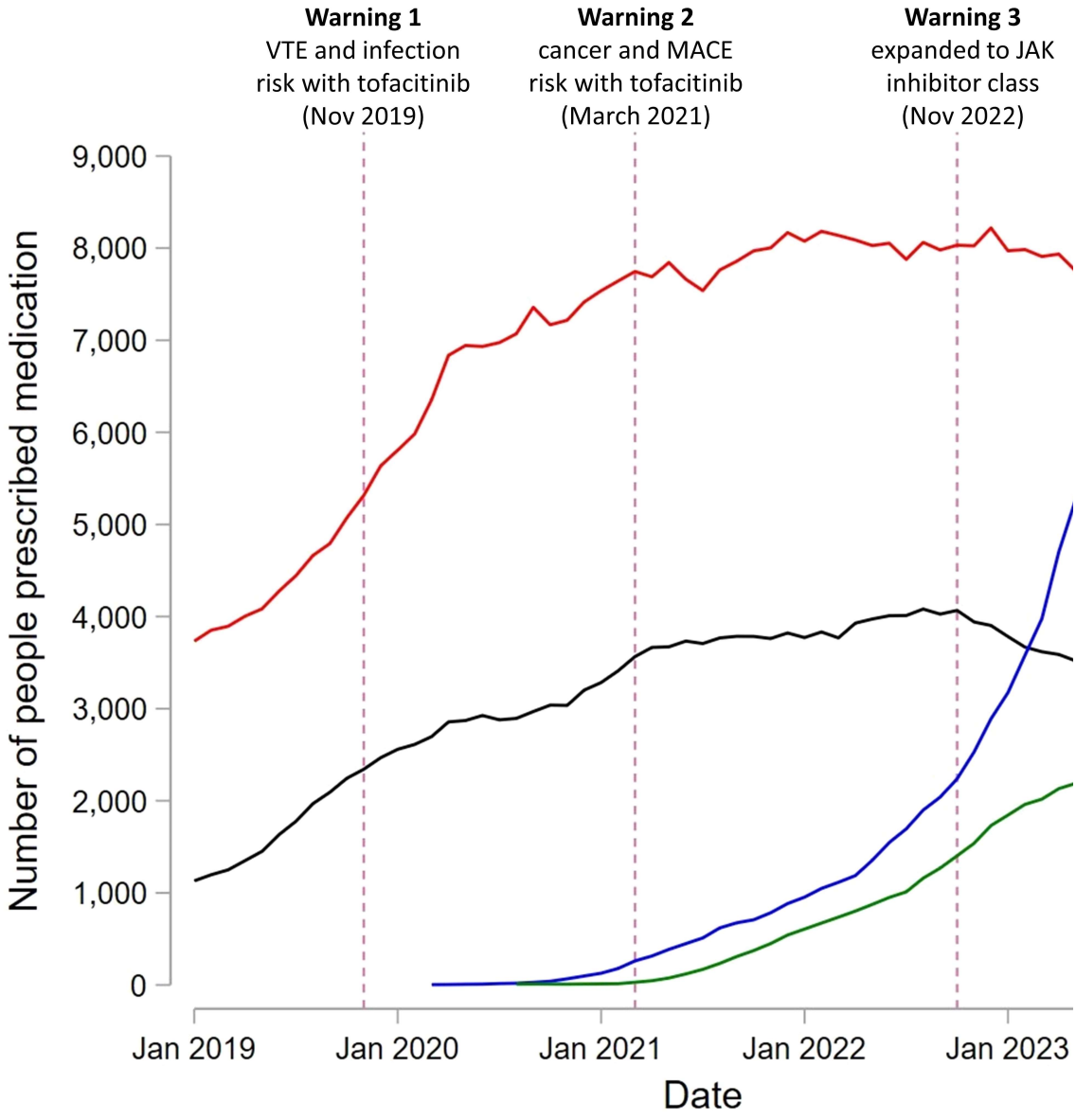
In 2017, the JAK inhibitors (JAKi), baricitinib and tofacitinib, were launched in Europe for the treatment of rheumatoid arthritis (RA). This was followed by the approval of upadacitinib and filgotinib. Licenced indications for the JAKi class have since expanded to include psoriatic arthritis, axial spondyloarthritis, juvenile idiopathic arthritis, inflammatory bowel disease, and atopic dermatitis, with indications differing widely for individual JAKi medications (see Supplementary Information).

In November 2019, the European Medicines Agency (EMA) issued a warning that tofacitinib could increase the risk of venous thromboembolism (VTE) in high-risk patients and serious infections in older adults, following interim data from the ORAL Surveillance trial.[1 2] In March 2021, the EMA issued a further warning concerning safety signals for major adverse cardiovascular events (MACE) and malignancies with tofacitinib, compared with TNF inhibitors, from ORAL Surveillance.[3] In November 2022, the EMA expanded this warning to include baricitinib, upadacitinib and filgotinib, recommending that JAKi should only be prescribed in higher risk patients if no suitable alternatives are available.[4]

It remains unclear how sequential safety warnings have impacted prescribing for JAKi at a population-level. We performed an ecological study to evaluate this, using nationwide prescribing data available in England (see Supplementary Information for more detailed methods).[5] Monthly dispensed volumes of tofacitinib, baricitinib, upadacitinib and filgotinib for combined treatment indications were aggregated from all hospitals in the English National Health Service between January 2019 and August 2023. Dispensed volumes were standardised using WHO Defined Daily Doses, and converted to estimated numbers of people prescribed each medication. Interrupted time-series analyses (ITSA) were performed to compare prescribing trends before and after sequential EMA warnings were issued.

Between January 2019 and August 2023, the number of people prescribed JAKi in England quadrupled, from 4,792 to 19,985 patients, respectively (Supplementary Figure S1). Underlying this increase were marked differences in prescribing trends for individual JAKi (Figure 1 and Supplementary Figure S2).

Figure 1. Prescribing trends for JAK inhibitors in England between January 2019 and August 2023.



Trends in the estimated number of people prescribed tofacitinib, baricitinib, upadacitinib or filgotinib for combined treatment indications in England between January 2019 and August 2023. Sequential safety warnings issued by the European Medicines Agency are denoted by vertical dashed lines. Variations in prescribing have been averaged over 3 months (see Supplementary Information, and Supplementary Figure S2 for trends without smoothing).

Following the EMA warning on VTE and infection risk with tofacitinib (November 2019), the rate of increase in tofacitinib prescribing slowed, from 146 additional patients/month to 56 additional patients/month ($p<0.001$) (Supplementary Figure S3). Tofacitinib prescribing slowed further after the EMA issued a warning on cancer and MACE risk with tofacitinib in March 2021 (from 56 to 24 additional patients/month; $p=0.009$), followed by a large decrease after the pan-JAKi warning was issued in October 2022 (from 24 additional patients/month to 63 fewer patients/month; $p<0.001$).

Baricitinib prescribing trends remained similar following the initial EMA tofacitinib safety warning (157 additional patients/month, pre-warning vs. 155 additional patients/month, post-warning; $p=0.93$), but slowed significantly following the second tofacitinib safety warning (from 155 to 23 additional patients/month; $p<0.001$), before decreasing sharply after the pan-JAKi warning (from 23 additional patients/month to 82 fewer patients/month; $p<0.001$) (Supplementary Figure S4).

In contrast, prescriptions for upadacitinib and filgotinib have continued to increase despite pan-JAKi safety warnings: upadacitinib prescribing accelerated after the EMA's pan-JAKi warning (94 additional patients/month, pre-warning vs. 556 additional patients/month, post-warning; $p<0.001$) (Supplementary Figure S5), while the rate of increase in filgotinib prescribing continued unchanged (67 vs. 70 additional patients/month; $p=0.76$) (Supplementary Figure S6).

Numerous factors in addition to safety will have contributed to the observed trends in JAKi prescribing: licenced indications have expanded more rapidly for some JAKi than others (see Supplementary Information); pharmacological properties and selectively vary widely between individual JAKi medications, which could influence prescribing choice; and safety considerations may also differ between treatment indications, depending on patient and disease characteristics (e.g. for RA vs. atopic dermatitis). Importantly, however, our findings highlight that the prescribing of upadacitinib and filgotinib has increased regardless of safety warnings being issued for the JAKi class as a whole. This may reflect clinicians perceiving safety risks as being attributable only to those medications for which safety signals have been directly observed.[1 6 7] Comparative data are not yet available in sufficient volume to evaluate these rare events for upadacitinib and filgotinib. Only time will tell whether in-vitro JAK-selectivity differences translate into meaningful differences in safety profile. Until then it is timely to recall Carl Sagan's quote: "Absence of evidence is not evidence of absence".

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Declarations of interest

JBG has acted in an advisory role to many pharmaceutical companies (listed below), including to provide specific advice on safety with JAK inhibition for the purposes of regulatory review. No authors received funding for this article, and there was no industry involvement or oversight for any stage of this project. JBG has received honoraria from Abbvie, Biovitrum, BMS, Celgene, Chugai, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Roche, Sanofi, Sobi and UCB. MDR has received honoraria from AbbVie, Lilly, Galapagos, Menarini and Viforpharma, advisory board fees from Biogen, and support for attending educational meetings from Lilly, Pfizer, Janssen and UCB. APC has received grant funding from BMS, and consulting fees from BMS, Abbvie and GSK/Galvini. KB has received grant funding from NIHR, honoraria from UCB and Viforpharma, and educational support from UCB. No other authors reported relationships or activities that could appear to have influenced the submitted work.

Data availability and sharing

All data utilised in this study are freely available online within the provided reference list, and can be shared upon reasonable request.

Ethical approval

All data utilised in this study are publicly available; as per UK HRA guidelines, no ethical approval was required.

Patient and public statement

There was no patient or public involvement in this study.

Contribution statement

Contributions are as follows: Conceptualisation: MDR, JBG, SN; Methodology: MDR, JBG, SN, SML, KB, MAA, ZY; Formal analysis: MDR, JBG, SN, EA, BW, ZY; Writing – original draft: MDR, JBG; Writing – revising, review and editing: all authors. All authors read and approved the final manuscript. MDR and JBG are the guarantors for the article, and accept full responsibility for the work and/or the conduct of the study, and controlled the decision to publish. MDR and JBG directly accessed and verified the underlying data reported in the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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