Correspondence on 'EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update'

We read with interest the recently published European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis (PsA) with pharmacological therapies[1] and the associated systematic literature research (SLR)[2]; we welcome the clarity that they offer for patient care.

We would like to bring three points to your readers' attention to correct and clarify the narrative supporting Recommendation 7 (Janus kinase (JAK) inhibitors).

Recommendation 7 states: "… Our SLR indicated tofacitinib may have similar efficacy as the TNFi adalimumab for joint involvement, but numerically lower efficacy in skin psoriasis.[1,15,72] … Safety signals exist for some infections, especially herpes zoster, as well as a recent signal for deep vein thrombosis especially with a high dose of tofacitinib which is not approved for PsA, but also the usual 5 mg twice daily dose particularly in those with cardiovascular risk factors and older patients.[15,72,73]"

Regarding the statement: "… as well as a recent signal for deep vein thrombosis especially with a high dose of tofacitinib which is not approved for PsA …":

We would like to respectfully correct this statement, as this signal was seen for pulmonary embolism (PE) rather than deep vein thrombosis (DVT); this was observed in the 10 mg twice daily dose of tofacitinib, which is not approved for PsA.

In February 2019, during a routine safety analysis of Study A3921133 (NCT02092467; database not locked, data not yet source-verified or subjected to standard quality-check procedures that occur at the time of database lock, therefore may be subject to change), an ongoing postauthorisation safety surveillance study for tofacitinib in patients with rheumatoid arthritis (RA) aged ≥50 years and with one or more cardiovascular risk factor, the independent tofacitinib Data Safety Monitoring Board reported a statistically increased incidence of PE events in patients receiving tofacitinib 10 mg twice daily versus tumour necrosis factor inhibitors (TNFi). The incidence of venous thromboembolism (VTE; PE or DVT) from this ad hoc safety analysis of Study A3921133 has been reported as an identified risk (adverse drug reaction) in the Summary of Product Characteristics (SmPC) for tofacitinib (table 1).[3]

Regarding the statement: "… but also the usual 5 mg twice daily dose particularly in those with cardiovascular risk factors and older patients.[15,72,73]":

The SLR publication states: "while no venous thromboembolic events or pulmonary embolisms were observed in patients with PsA treated with tofacitinib or filgotinib,[13,55] such events were seen in other indications when tofacitinib, baricitinib and upadacitinib were used, especially in an ongoing study on patients with RA with high cardiovascular risk (tofacitinib study A3921133); warnings in these regards were issued by regulators, especially with respect to patients with a high risk for venous thromboembolic events.[56,57]"[2]

There were no statistically significant differences in the incidence rates (IRs) for DVT among tofacitinib 5 mg twice daily (the licenced dose), tofacitinib 10 mg twice daily and TNFi (table 1). Additionally, the difference in IRs for PE between tofacitinib 5 mg twice daily and TNFi was not statistically significant. Based on the totality of available information, including, but not limited to, analyses of Study A3921133 data, VTE has been determined to be an important identified risk for tofacitinib treatment. Consequently, the tofacitinib SmPC was updated following the European Commission decision on 31 January 2020,[4] to include additional text in the 'Special warnings and precautions for use', 'Undesirable effects' and 'Pharmacodynamic properties' sections pertaining to VTE.[3] We believe that it is important to clarify for your readers that the SmPC updates related to VTE are relevant for the treatment of patients with any condition for which tofacitinib is indicated, including patients with RA or PsA.

Regarding the statement: "tofacitinib may have similar efficacy as the TNFi adalimumab for joint involvement, but numerically lower efficacy in skin psoriasis,[1,15,72]"

Consistent with the results of OPAL Broaden[5] and the SLR publication,[2] tofacitinib has been shown to have similar efficacy to adalimumab in joint and skin psoriasis.

Results from OPAL Broaden show that the proportion of patients achieving ≥75% improvement in the Psoriasis Area and Severity Index at month 3 (secondary endpoint) was 43% for tofacitinib 5 mg twice daily and 39% for adalimumab 40 mg every other week (the study was not designed to compare non-inferiority or superiority between tofacitinib and adalimumab).[5] These results are accurately reported in table 3 in the SLR publication, which also states: "tofacitinib was superior to placebo in csDMARD-IR patients and, although not formally tested, exhibited numerically similar results as adalimumab in OPAL Broaden".[2] To inform understanding of the available data from the tofacitinib clinical programme, we respectfully draw this inaccuracy in the recommendations to the attention of your readers.

Recognising the independence of the EULAR Taskforce from pharmaceutical companies, we seek to correct and clarify the information about JAK inhibitors, and specifically tofacitinib, within the EULAR recommendations, and to provide your readers with the correct information to inform patient care.

Table 1 IRs and HRs of PE and DVT for tofacitinib 5 and 10 mg twice daily versus TNFi (95% CI) from the ad hoc safety analysis of ongoing Study A3921133 (data cut-off: February 2019; database not locked; data not yet source-verified or subjected to standard quality-check procedures that would occur at the time of database lock and may therefore be subject to change)

Safety endpoint		Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily	TNFi
PE	IR (95% CI)	0.27 (0.12 to 0.52)	0.54 (0.32 to 0.87)	0.09 (0.02 to 0.26)
	HR versus TNFi (95% CI)	2.99 (0.81 to 11.06)	5.96 (1.75 to 20.33)	–
DVT	IR (95% CI)	0.30 (0.14 to 0.55)	0.38 (0.20 to 0.67)	0.18 (0.07 to 0.39)
	HR versus TNFi (95% CI)	1.66 (0.60 to 4.57)	2.13 (0.80 to 5.69)	–
Subgroup analysis in patients with VTE risk factors				
PE	HR versus TNFi (95% CI)	3.92 (0.83 to 18.48)	9.14 (2.11 to 39.56)	–

DVT, deep vein thrombosis; IR, incidence rate (unique patients with events per 100 patient-years); PE, pulmonary embolism; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

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