

**Table 4: Summary of evidence and answers to the questions addressed in this systematic review**

**1. What is the efficacy of TCZ in reducing the frequency and severity of FMF attacks?**

Using the Eurofever/PRINTO FMF classification criteria, the majority of patients included in the presented trials do not meet the classification criteria for classical FMF. The heterogeneity of reported efficacy results across trials makes it difficult to assess the overall efficacy of TCZ.

Therefore, **there is still insufficient evidence to recommend IL6 inhibition in FMF. IL1 $\beta$  inhibitors remain the first choice in colchicine-resistant disease or colchicine intolerance. Case series and reports suggest that TCZ may be of interest in some selected FMF patients with established AA amyloidosis and resistance to colchicine and to IL-1 inhibitors, but further studies are needed to confirm this.**

**2. What is the safety profile of TCZ in patients with FMF?**

The safety profile of TCZ in FMF patients does not appear to differ from that of other rheumatic diseases. **The overall safety profile of TCZ appears to be very safe. No data were available on the use of TCZ in pregnant or breastfeeding patients.**

**3. What is the optimal administration regimen of tocilizumab (TCZ) in FMF patients, and how does it affect treatment outcomes?**

Only the Japanese double-blind RCT by Koga et al. administered TCZ in a subcutaneous regimen at the usual dose of 162 mg/week. The German double-blind RCT by Henes et al. and both retrospective studies administered TCZ in an intravenous regimen at a dose of 8 mg/kg. No studies have compared SC with IV administration. Therefore, **there are currently insufficient data to assess the potential superiority of one route of administration over the other.**

**4. What are the gaps in the current evidence regarding the use of tocilizumab (TCZ) in FMF, and what further research is needed in this area?**

Our findings highlight **the importance of using the Eurofever/PRINTO classification criteria for FMF in future trials**, which take into account mutation status, ethnicity and clinical parameters, **in order to have homogeneous patient cohorts in this genetically complex disease.** Furthermore, our results emphasize **the need for homogeneous endpoint definitions based on official definitions of colchicine resistance, intolerance and clinical and biological complete and partial disease remission for future RCTs.** These points are mandatory to **better assess the treatment efficacy and safety of different therapies** in this complex disease and to help **derivate specific disease activity scores.**

Only the German study by Henes et al. looked at improvement in quality of life as assessed by the FFbH score and found no significant difference at week 16 in the TCZ arm. **Further research is also needed to better assess quality of life measures, adherence and patient satisfaction**, as almost no data on these potentially important outcomes were found in the reported trials.

**5. Are there any particularities in pediatric patients compared to adult FMF patients regarding the indication, efficacy and safety of TCZ?**

There was no available data on the use of TCZ in pediatric FMF.

