On the other hand, several case studies reported an improvement in renal function for patients with amyloidosis following anakinra treatment [129,134]. The use of anakinra during pregnancy was shown to be safe [135,136] and is currently recommended in colchicine-resistant women.

The most common side effect is injection site reaction [137]. Albeit uncomfortable, these usually resolve within 2–3 weeks of treatment initiation; however, they may be so severe to prompt a patient to interrupt treatment [138].

As for other anti-cytokine treatments, a major concern is the risk of infection. Nevertheless, in comparison to other biologic agents, anakinra has an unparalleled safety benefit deriving from a short half-life, and the effect duration and has demonstrated a remarkable record of safety [139].

11.2. Rilonacept

Rilonacept is a very high affinity "cytokine trap" consisting of fusions between the constant region of IgG and the extracellular domains of two distinct cytokine receptor components involved in binding the cytokine [140]. It is administered weekly with an injection.

The first randomised placebo-controlled study on FMF with an anti-IL-1 agent was performed with rilonacept. The study included 12 patients and rilonacept significantly reduced the number of FMF attacks and had an acceptable safety profile, with no serious side effects associated with this drug [141].

11.3. Canakinumab

Canakinumab is the only FDA-approved cytokine blocker for the treatment of colchicine-resistant FMF in the United States [142]. Its long half-life allows a monthly subcutaneous administration.

The first report in the literature on the successful administration of canakinumab in a patient with FMF and chronic arthritis after failing anakinra, etanercept and low-dose prednisone, and methotrexate was published in 2011 [143]. A significant decrease in proteinuria in the amyloidosis-complicated FMF patients was observed [144]. All the series reported that patients benefit from canakinumab [145–147] and others, also in terms of quality of life [63].

The efficacy of the treatment was confirmed when randomised against a placebo in a cohort of colchicine-resistant FMF patients together with TRAPS and mevalonate kinase deficiency (MKD) patients [148]. A complete response occurred in 71% of FMF patients when treated with canakinumab (150 or 300 mg subcutaneously every 4 weeks). Patients who did not have a complete response had a lower number of days with fever per year. When an extended dosing regimen (canakinumab every 8 weeks) was evaluated, the absence of flares was maintained in approximately half the patients with colchicine-resistant FMF. In this study, no deaths, opportunistic infections, or cancers were reported.

In all three cohorts, infections were more numerous in the canakinumab group than in the placebo group, serious infections being rare (7.4 per 100 patient-years). Three patients had to discontinue treatment because of neutropenia [148]. The long-term efficacy and safety of canakinumab in the phase 3 cluster trial of the same study were recently reported [149].

12. Anti-IL-6 Drugs

IL-6 is elevated in the serum of FMF patients during attacks, and its potential as a biomarker to distinguish between acute phase and remission [150] and drug target was investigated. Tocilizumab (TCZ) is a humanised monoclonal anti-IL-6 receptor antibody, binding to soluble and membrane receptors and down-regulating IL-6 synthesis, and as a consequence, possibly suppressing SAA production. Indeed, the result from a series of 12 patients with AA amyloidosis secondary to FMF treated with TCZ, showed an improvement in attacks [151].

The long-term safety of TCZ is now being investigated in a Japanese multicentre placebo-controlled, randomised, double-blind trial on colchicine-resistant and colchicine-intolerant FMF [152].

Conclusive Remarks and Future Perspective

In conclusion, Familial Mediterranean Fever (FMF) is the first inflammatory condition for which a causative gene was identified and represents a prototype of a monogenic autoinflammatory disease condition. In recent years, significant progress has been made in understanding the pathogenic mechanisms related to this condition. Early diagnosis and prompt treatment with colchicine can effectively manage symptoms and prevent complications.

Future research efforts should focus on developing more effective therapies for FMF patients who are unresponsive to colchicine. Further studies are also needed to identify new genetic mutations that contribute to FMF and to explore the possible association between FMF and other diseases. Moreover, the development of biomarkers for monitoring disease progression and response to therapy would be beneficial for improving the clinical management of FMF. In addition, genetic counselling and family screening programs should be implemented to identify asymptomatic carriers and prevent the transmission of the disease to future generations. In summary, while significant progress has been made in understanding and treating FMF, there is still much to be done to improve patient outcomes and quality of life. With continued research efforts and collaboration among healthcare professionals, we can work toward better management and ultimately a cure for this condition.

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