dupilumab in head-to-head clinical trials.[9,17,56,57] Lower doses (upadacitinib 15 mg daily, abrocitinib 100 mg daily) are somewhat less efficacious than higher doses but still show excellent improvement in the signs and symptoms of AD.[9] Because of potential safety concerns, it is recommended by the FDA and other regulatory bodies that these medications be started at their lower doses (Table IV), particularly in older adults, a population considered to be at higher risk for adverse events (Supplementary Table VI, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1).

Baricitinib, which preferentially inhibits both JAK-1 and -2, is also effective for AD.[32-36,59] It is approved in Europe for the treatment of moderate to severe AD, and is approved and available in the US for other immune-mediated conditions, but is not approved by the FDA to treat AD. While no head-to-head clinical trials were done, network meta-analysis suggests baricitinib is less efficacious than upadacitinib and abrocitinib.[9]

Based on safety data from other JAK inhibitors used in other populations, the FDA applied warnings of increased risk of serious heart-related events, cancer, blood clots, and death for the JAK inhibitor class.[60] In a noninferiority trial of people with active rheumatoid arthritis despite methotrexate treatment, aged 50 years and older, and with at least one cardiovascular risk factor, 1455 patients were randomized to either tofacitinib (a JAK-1 and -3 inhibitor) or a tumor necrosis alpha inhibitor and followed for a median of 4 years.[61] Major adverse cardiovascular events and malignancies were higher among people randomized to tofacitinib.[61] Importantly, that trial's population and therefore baseline risk for serious adverse events differs substantially from most people initiating systemic treatment for AD, and tofacitinib is a different JAK inhibitor with less selective inhibition compared to the approved JAK-1 inhibitors for AD. Still, those safety signals warrant some caution when prescribing JAK inhibitors for AD, as serious adverse effects, including death and thromboembolic events, have occurred in clinical trials of AD patients. Other potential safety concerns with JAK inhibitors include an increased risk of serious and opportunistic infections, including herpes zoster.[26,31] When feasible, it is recommended to vaccinate for shingles before initiating a JAK inhibitor, particularly for older patients. In the US and Canada, the recombinant zoster vaccine (nonlive) is approved for immunocompetent adults ages 50 years and older as well as adults ages 19 years and older who are immunocompromised or will be taking medications that increase the risk of herpes zoster; use of JAK inhibitors is included in the latter category. Patients should also receive any other needed live vaccines before initiating treatment. It is recommended by the FDA to check complete blood count with differential, liver enzymes at baseline, and after initiation or dose-escalation (4 weeks for abrocitinib, and per routine management after baseline for upadacitinib); lipids should be checked only after initiation (4 weeks for abrocitinib, 12 weeks for upadacitinib); testing for viral hepatitis, tuberculosis, and pregnancy should be performed at baseline. The optimal frequency of ongoing lab monitoring required for patients who are continuously using JAK inhibitors is unclear.

Antimetabolites and immunosuppressants

Cyclosporine, methotrexate, azathioprine, and mycophenolate are the most commonly recommended older systemic therapies for AD. We gave each of these medications conditional recommendations based on low or very low certainty evidence (Supplementary Tables VII-XII, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1). Evidence was downgraded for risk of bias and imprecision due to small sample sizes. In one head-to-head clinical trial, cyclosporine was more effective than methotrexate for up to 16 weeks, after which they were similarly effective.[37] In another clinical trial, azathioprine and methotrexate had essentially identical efficacy through 12 weeks of treatment.[38] In a network meta-analysis, cyclosporine dosed between 3 and 5 mg/kg per day is more effective than methotrexate and azathioprine, which, in turn, are more effective than placebo, but with substantial uncertainty due to small sample sizes in the underlying clinical trials.[8,9]

There is less randomized trial evidence supporting the use of mycophenolate. One trial randomized patients who were already treated with cyclosporine during a run-in period to maintenance with either mycophenolate sodium or cyclosporine, with little difference in efficacy between the arms at 10 weeks.[40]

Cyclosporine, methotrexate, azathioprine, and mycophenolate require baseline and ongoing laboratory monitoring for adverse effects. Specific guidance can be found in the 2014 AAD guidelines.[4] Each of these medications can also increase the risk of serious infections. Additionally, each has its own specific potential end-organ toxicities. Among other effects, cyclosporine is most prominently associated with renal impairment and hypertension, methotrexate with liver damage, and azathioprine and mycophenolate with cytopenias. Cyclosporine is not suitable for long-term use, as the potential for renal damage increases with cumulative dose. We