

**Supplementary Table 2:** Summary of efficacy, safety, approved indications, and contraindications of treatment options for AD in Qatar

Treatment	Approved indications	Efficacy in AD	Safety in AD	Lab tests and monitoring	Contraindications and/or precautions
Dupilumab	<p>FDA approved for the following indications:</p> <ul style="list-style-type: none"> <li>Moderate-to-severe AD: Adults and children from 6 months to 5 years</li> <li>Severe asthma: Adults and children <math>\geq 6</math> years</li> <li>Eosinophilic esophagitis: Adults and children <math>\geq 12</math> years</li> <li>Chronic rhinosinusitis with nasal polyposis</li> <li>Adults with prurigo nodularis [24]</li> </ul> <p>EMA approved for the following indications:</p> <ul style="list-style-type: none"> <li>Moderate-to-severe AD: Adults and adolescents <math>\geq 12</math> years</li> <li>Severe AD: Children (6–11 years), who are suitable for systemic therapy [25]</li> </ul>	<p>Dupilumab is the first FDA-approved biologic drug that is licensed specifically to treat AD [4].</p>	<p>Dupilumab has a favorable safety profile. However, conjunctivitis and keratitis are found to occur more frequently in patients receiving dupilumab [24].</p> <p>Dupilumab has been shown to be safe for treating adults with moderate-to-severe AD for up to 3 years [38].</p>	<p>No laboratory test at baseline or follow-up is required [24].</p>	<p>Using dupilumab is contraindicated in patients who are hypersensitive to it or any of its excipients [24].</p> <p>The following precautions should be taken:</p> <ul style="list-style-type: none"> <li>Not recommended to be used for treating acute asthma symptoms</li> <li>Corticosteroid medication should not be discontinued abruptly upon initiation of dupilumab treatment.</li> <li>It should be discontinued in case of hypersensitivity, eosinophilic cases, helminth infection, conjunctivitis, and keratitis-related events</li> <li>Patients who have pre-existing helminth infections should be treated before starting treatment with dupilumab.</li> <li>Asthma treatment should not be stopped abruptly in patients who have co-existing asthma.</li> <li>Attenuated and live vaccines should be avoided while on dupilumab [24].</li> </ul>
Baricitinib	<ul style="list-style-type: none"> <li>Approved by the FDA only for treating RA [32].</li> <li>Approved by EMA for treating moderate-to-severe AD in adult patients, moderate-to-severe RA, and severe alopecia areata [33].</li> </ul>	<p>Patients with moderate-to-severe AD experienced an improvement in clinical signs and a rapid reduction in induced itching sensation within 16 weeks of baricitinib treatment [33].</p>	<p>Baricitinib is relatively safe.</p> <p><b>Black box warning as per FDA [32]:</b></p> <ul style="list-style-type: none"> <li>Risk of serious fungal, bacterial, viral, and opportunistic infections including TB.</li> <li>Risk of sudden cardiovascular death.</li> <li>Risk of malignancy.</li> <li>Risk of thrombosis.</li> </ul> <p><b>Warnings as per EMA [33]:</b></p> <ul style="list-style-type: none"> <li>Increased risk of infections, such as upper respiratory tract infection.</li> </ul>	<p>Required laboratory tests and monitoring:</p> <ul style="list-style-type: none"> <li>Monitoring of the lipid parameters should be conducted at 12 weeks after starting treatment and later as per the international clinical guidelines for hyperlipidemia</li> <li>Blood parameters such as neutrophil count, lymphocyte count, hemoglobin level, and level of hepatic transaminase should be monitored before treatment initiation and followed thereafter during a routine examination [33].</li> </ul>	<p>As per the EMA, baricitinib is contraindicated during pregnancy and in patients with hypersensitivity to baricitinib [33].</p>



			<ul style="list-style-type: none"> <li>• Should not be prescribed to patients who have active TB.</li> <li>• Risk of venous thromboembolism, hematological abnormalities, viral reactivation, malignancies</li> <li>• Increased blood lipid parameters and hepatic transaminase enzyme levels</li> </ul>		
Upadacitinib	<ul style="list-style-type: none"> <li>• Upadacitinib is approved by the FDA to treat patients with moderate-to-severe RA not responsive to methotrexate [27].</li> </ul> <p>Upadacitinib is approved by the EMA for the following indications:</p> <ul style="list-style-type: none"> <li>• To treat adults and adolescents (≥12 years) with moderate-to-severe AD who are eligible for systemic therapy</li> <li>• To treat adult patients with moderate-to-severe RA or active psoriatic arthritis, not responding adequately to one or more disease-modifying antirheumatic drugs</li> <li>• To treat adult patients with active ankylosing spondylitis not responding adequately to conventional therapy [28]</li> </ul>	Upadacitinib (15 mg and 30 mg) was effective in treating moderate-to-severe AD in patients >12 years [28].	<p><b>Black box warning as per FDA [27]:</b></p> <ul style="list-style-type: none"> <li>• Serious bacterial, viral, and invasive fungal infections or TB</li> <li>• Lymphoma and other malignancies have been observed</li> <li>• Risk of thrombosis</li> </ul> <p><b>Safety as per EMA [28]</b></p> <ul style="list-style-type: none"> <li>• Serious infections and sometimes even risk of mortality</li> <li>• Risk of pneumonia and cellulitis</li> <li>• Risk of opportunistic infections, such as TB, multi-dermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis</li> </ul>	<p><b>Required laboratory tests and monitoring:</b></p> <ul style="list-style-type: none"> <li>• Blood parameters, such as neutrophil count, lymphocyte count, and hemoglobin level, should be evaluated at baseline and within 12 weeks after starting treatment. Based on individual patient management, evaluations should be conducted thereafter.</li> <li>• Hepatic transaminase should be measured at baseline and later as per routine management.</li> <li>• Lipid level should be monitored at 12 weeks after starting the treatment and later as per the international clinical guidelines for hyperlipidemia [28].</li> </ul>	<p>As per the FDA label, there is no contraindication for upadacitinib. FDA warns against the following: Use in patients with active, serious infections and hepatitis B or C infections; active TB patients; and patients who may be at an increased risk of gastrointestinal perforation [27].</p> <p>As per the EMA, upadacitinib is contraindicated in patients with hepatic disorder, active severe infections, active tuberculosis, pregnancy, and in patients who are hypersensitive to the active substance of upadacitinib or any of the excipients [28].</p>



Abrocitinib	<ul style="list-style-type: none"> <li>Abrocitinib is approved by the FDA to treat patients (&gt;18 years) with refractory, moderate-to-severe AD who do not respond to biologics and other therapies [31].</li> <li>Abrocitinib is approved by the EMA to treat adults with moderate-to-severe AD, who are eligible for systemic therapy [30].</li> </ul>	The combination of oral abrocitinib with topical therapy was effective for adolescents with moderate-to-severe AD [39].	<p>Black box warning as per FDA:</p> <ul style="list-style-type: none"> <li>Risk of bacterial, fungal, viral, and opportunistic infections, including tuberculosis</li> <li>Sudden cardiovascular death and MACE</li> <li>Malignancies</li> <li>Thrombosis [31]</li> </ul> <p>The safety profile of abrocitinib in children under 12 years of age has not been established. The most common serious adverse reactions are infections [30].</p>	Complete blood count, which includes absolute neutrophil count, platelet count, absolute lymphocyte count, and hemoglobin should be evaluated before starting the treatment, 4 weeks after treatment, and thereafter routinely as per patient management [30].	<p>As per the FDA, contraindicated in patients who are on antiplatelet therapies, excluding the patients who are on low-dose aspirin. FDA warns against using abrocitinib in patients with chronic or recurrent infection, with a history of a serious or an opportunistic infection, and active tuberculosis [31].</p> <p>As per the EMA, abrocitinib is contraindicated in patients with hepatic disorder, severe (Child–Pugh C) hypersensitivity to abrocitinib or its excipients, active systemic infections like TB, and during pregnancy and breastfeeding [30].</p>
Tralokinumab	<ul style="list-style-type: none"> <li>Tralokinumab is approved by the FDA to treat moderate-to-severe AD in adults who have not responded adequately to topical prescription therapies or when these therapies are not advisable [34].</li> <li>As per the EMA, tralokinumab is approved to treat moderate-to-severe AD in adults who are suitable for systemic therapy [35].</li> </ul>	Tralokinumab is effective in the treatment of adults with moderate-to-severe AD [40].	<ul style="list-style-type: none"> <li>The safety and tolerability profile of tralokinumab is acceptable in adults with moderate-to-severe AD [34].</li> <li>As per the EMA, the most frequently observed safety concerns were injection-site reactions, upper respiratory tract infections, and conjunctivitis [35].</li> </ul>	No laboratory tests or monitoring are required [35].	<ul style="list-style-type: none"> <li>Tralokinumab is contraindicated in patients who are hypersensitive to tralokinumab or any of its excipients and in individuals with active helminth infections [34,35].</li> <li>As per the FDA, tralokinumab increases the risk of getting an infection after live vaccination [34].</li> </ul>
Cyclosporine A (CSA)	<ul style="list-style-type: none"> <li>Indicated to treat severe psoriasis, RA, and prophylaxis of organ rejection in transplantations [36].</li> <li>Off-label indication: For the short-term treatment of adults with severe refractory AD [12,37].</li> </ul>	<p>The efficacy of CSA in AD has been described in several RCTs [41].</p> <p>Significant improvement in clinical symptoms is observed in adults and pediatric patients with AD when treated with CSA. Although CSA is reported to be more effective at</p>	<p><b>Black box warning as per FDA:</b></p> <p>Risk of increasing susceptibility to infection and developing neoplasia. Risk of development of lymphoma and other neoplasms may result from the increase in the degree of immunosuppression in transplant patients [36,37].</p>	Liver and renal functions should be evaluated repeatedly by measuring serum bilirubin, serum creatinine, and liver enzymes. The levels of lipids, potassium, and magnesium should also be monitored [36,37].	<ul style="list-style-type: none"> <li>In patients who are hypersensitive to CSA or any of the excipients of CSA [36].</li> <li>In treating patients with RA and psoriasis under the conditions mentioned below: Uncontrolled hypertension; abnormal renal function; primary or secondary immunodeficiency, excluding autoimmune disease, uncontrolled infections, and malignancy [36].</li> </ul>



		higher doses (5 mg/kg body weight), the treatment should be initiated at lower doses (3 mg/kg body weight) by adjusting the individual minimal dose in a stepwise manner. Most side effects are dose related [41].			
Glucocorticosteroids	<ul style="list-style-type: none"> <li>Used as an immunosuppressive or anti-inflammatory agent for the following conditions: Gastrointestinal, allergic, dermatological, hematologic, ophthalmologic, respiratory, nervous system, rheumatologic, renal, specific infectious diseases, and organ transplantation for treating certain endocrine diseases [42].</li> </ul>	Systemic corticosteroids (SCS) are rapidly effective. As SCS are associated with long-term side effects, they should only be used for 1–2 weeks for severe acute exacerbation [4].	Long periods of treatment with SCS should be avoided since they are associated with the risk of severe side effects [4].	Regular blood pressure monitoring, laboratory evaluations, and X-rays of the chest should be obtained during prolonged therapy with glucocorticoids like prednisone [42].	Contraindicated in patients who are hypersensitive to prednisone or any of the excipients [42].
Azathioprine (AZA)	<ul style="list-style-type: none"> <li>As per the FDA, AZA is used to prevent rejection in renal homotransplantation and RA [43].</li> <li>As per the EMA, AZA can be used along with immunosuppressive agents for the prophylaxis of transplant rejection in patients who have received allogeneic transplants of kidney, liver, heart, lung, or pancreas. It is also used to treat multiple sclerosis and generalized myasthenia gravis [44].</li> </ul>	AZA is recommended as a systemic agent to treat refractory AD. Patients on azathioprine monotherapy for AD experience improved QoL and clinical presentation [45].	The side effect observed in treating AD patients with AZA is similar to those who have been treated for cutaneous indications [45].	Complete blood counts, which also include platelet counts, should be assessed weekly during the first 8 weeks of treatment. It should be monitored more frequently if used in elderly patients, or high doses are used, or used in patients with renal or hepatic function impairment. Liver function tests should be done repetitively while treating with AZA. After 8 weeks, blood counts should be evaluated every month or at intervals $\leq 3$ months [44].	<b>Absolute</b> <ul style="list-style-type: none"> <li>Allergy to AZA during conception or during pregnancy</li> <li>Serious active infection</li> </ul> <b>Relative</b> <ul style="list-style-type: none"> <li>Simultaneous use of allopurinol</li> <li>Previously treated with chlorambucil or cyclophosphamide [46]</li> <li>Contraindicated in patients with hypersensitivity to AZA, live vaccinations, and lactating women [44]</li> </ul>



MMF	<ul style="list-style-type: none"> <li>As per the FDA and EMA, MMF +corticosteroids and CSA can be used for the prophylaxis of acute transplant rejection in patients who have received allogeneic, hepatic, cardiac, or renal, transplants [47,48].</li> </ul>	<p>For patients with refractory AD, MMF can be used as an alternative therapy. The efficacy of MMF is variable. In a study, 85% of patients have improved within the first month of treatment and 50% of patients were cleared of their disease and could discontinue the treatment [46].</p>	<p>MMF is usually well tolerated. The most frequently observed side effects of MMF are infection, pregnancy loss, lymphoma, abdominal cramping, diarrhea, vomiting, leukopenia, and nausea [46,47]. As per the EMA, the following are the side effects: Malignancies, infections, blood and lymphatic disorders, pure red cell aplasia, gastrointestinal disorders, etc [48].</p>	<p>In the first month of treatment, blood counts should be evaluated weekly, then for the second and third months of treatment twice monthly, and later monthly throughout the first year [48].</p>	<ul style="list-style-type: none"> <li>As per the FDA, females of childbearing age should be warned regarding the risk associated with MMF [47].</li> <li>Patients receiving MMF should be monitored for neutropenia [47].</li> <li>Contraindicated in patients who are hypersensitive to MMF, mycophenolic acid, or any component of the drug product, during pregnancy and breastfeeding [47,48].</li> </ul>
MTX	<ul style="list-style-type: none"> <li>As per the FDA and EMA, MTX is indicated for neoplastic diseases, psoriasis, and RA, including polyarticular course juvenile RA. It is also used as a maintenance treatment of acute lymphoblastic leukemia in patients above 3 years of age [49,50].</li> </ul>	<p>MTX showed satisfactory effectiveness like AZA [46].</p>	<p>MTX is often tolerated well and can be given intramuscularly, subcutaneously, and orally [46,50]. The most frequently reported side effect of MTX is dose related. Most serious adverse reactions are pulmonary toxicity, anaphylactic shock, bone marrow suspension, hepatotoxicity, neurotoxicity, renal toxicity, thromboembolic events, and Stevens–Johnson syndrome [50].</p>	<p>Complete blood count, serum albumin, bilirubin, liver enzymes, and renal function test are recommended for patients before the initiation of treatment or resumption of treatment after a recovery period. Tests for TB and hepatitis B and C should be conducted to exclude such patients. During treatment, serum albumin should be monitored in the first two weeks for a month and later the frequency of testing should be decided based on the leukocyte count and stability of the patients; minimum once monthly for the next 6 months followed by every 3 months [50].</p>	<ul style="list-style-type: none"> <li>MTX can lead to fetal death or teratogenic effects when given during pregnancy [49].</li> <li>Contraindicated in patients with severe hepatic and renal impairment; alcohol abuse; severe, acute, or chronic infections such as TB and HIV; hypersensitive to active substance or any of its excipients, immunodeficiency; ulcers of the oral cavity and known active gastrointestinal ulcers; stomatitis, and simultaneous vaccination with live vaccines [50].</li> </ul>



Phototherapy	<ul style="list-style-type: none"> <li>• Phototherapy is used when patients do not respond to first-line therapy, such as topical steroids, calcineurin inhibitors, and emollients [46].</li> <li>• The ETFAD recommends simultaneous administration of NB-UVB or medium-dose UVA along with TCS or selected systemic therapy for treating AD [4].</li> </ul>	Acute and chronic AD in children and adults can be treated with phototherapy [46].	<p>Although phototherapy-related adverse events are not known, it is assumed to be low [46].</p> <ul style="list-style-type: none"> <li>• Under well-controlled settings, this therapy has a low side effect (burning, erythema, tenderness, and pruritus) [46].</li> <li>• Long-term effects (skin aging and cancer) dependent on the frequency and duration of long-term treatment should be limited according to guidelines [4,46].</li> </ul>	-	As the use of phototherapy is associated with the risk of nonmelanoma skin cancer and melanoma, it is not recommended in patients with syndromes that are associated with an increased risk of melanoma/nonmelanoma skin cancer [46].
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AD: Atopic dermatitis; AZA: Azathioprine; CSA: Cyclosporine; ETFAD: European Task Force on Atopic Dermatitis; EMA: European Medicines Agency; FDA: Food and Drug Administration; MACE: Major adverse cardiovascular events; MTX: Methotrexate; MMF: Mycophenolate mofetil; NB-UVB: Narrowband ultraviolet B; RA: Rheumatoid arthritis; SCS: Systemic corticosteroids; TB: Tuberculosis; TCS: Topical corticosteroids; UVA: Ultraviolet A; UVB: Ultraviolet B.