In patients with rheumatic diseases, the well-documented benefits of breastfeeding must be carefully weighed against the risks of medication exposure to the infant. Given the absence of placebo controlled studies, estimation of drug safety is based on small studies of drug levels in breast milk and infant serum, case reports of adverse events in breastfed infants, and theoretical considerations. Medications are transferred to breast milk primarily via diffusion. Those with short half-lives, high protein binding, and/or high molecular weights are less likely to cross into breast milk. In general, breast milk drug levels of less than 10% of the infant therapeutic dose or the maternal weight-adjusted dose are considered to be safe. Most medications have peak levels in breast milk 1-2 hours after maternal ingestion; avoiding nursing during this window may significantly reduce infant exposure.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Breast milk levels</th>
<th>Infant serum levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>TNF inhibitors</td>
<td>Low</td>
<td>Variable (initial elevation likely due to placental transfer not breastfeeding)</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IVIG)</td>
<td>Detected</td>
<td>Detected</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>High</td>
<td>Variable</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Low</td>
<td>No data</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Detected</td>
<td>No data</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Low</td>
<td>No data</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Non-anti-TNF monoclonal biologic agents</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

Table 1. Summary of safety data on the use of anti-inflammatory and immunosuppressive medication in lactation

COLOR CODING

Green  likely safe
Yellow possibly safe
Red  likely unsafe- avoid

Anti-inflammatory drugs available in the USA for the treatment of acute gout and for flare prophylaxis are non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids (CS), adrenocorticotropic hormone (ACTH, corticotropin) and interleukin-1 (II-1) inhibitors. Urate lowering drugs (ULDs) reduce serum urate (SU) levels and are given chronically with the target goal of lowering SU to ≤6mg/dl. Available ULDs include allopurinol, Febuxostat, probenecid and pegloticase. When prescribing drugs for gout one has to be mindful of the presence of comorbidities such as the metabolic syndrome, hypertension, dyslipidemia, cardiovascular disease, diabetes and chronic kidney disease (CKD) which are highly prevalent in gout patients.
Drug Safety Quarterly

Drug Safety and Lactation

Published series have reported low or undetectable levels of TNF inhibitors:

Tacrolimus: 
- 0.75% but increases with higher doses of glucocorticoids.
- If the maternal dose is greater than 20 mg per day, check infant drug levels and serum creatinine.

The active metabolite of azathioprine, 6-mercaptopurine (6-MP), has been found at low concentrations in breast milk. In a total of 14 infants evaluated in two case series, serum levels of 6-MP in neonatal blood were undetectable. No clinical or hematologic evidence of immunosuppression was noted in exposed infants.

Sulfasalazine: The concentration of sulfapyridine (SP), the metabolite of sulfasalazine, in breast milk may have been demonstrated to be 40-60% of the levels in maternal serum. Infant serum concentrations are low. Diarrhea has been reported in a nursing infant exposed to sulfasalazine; infants should be closely monitored for this complication. The medication should be avoided in premature infants and those with hyperbilirubinemia as SP can displace bilirubin.

TNF inhibitors: Published series have reported low undetectable levels of Etanercept, Adalimumab, and Infliximab in breast milk. Infant serum levels have been either undetectable or have declined to undetectable levels over 6 or 12 weeks post-partum in infants exposed in utero, despite continued breastfeeding. There are no published human data on breast milk or infant serum levels of Golimumab or Certolizumab pegol.

IVIG: One study of two mothers receiving IVIG for common variable immunodeficiency suggests transfer via breast milk. In a retrospective study of 108 pregnancies in patients with multiple sclerosis, IVIG use was not associated with adverse outcomes in breastfed infants.

Cyclosporine: Case reports and series suggest that breast milk concentrations of cyclosporine are high, often similar to maternal levels. In most reported cases, infant serum levels have been reassuringly undetectable. However, one infant was found to have therapeutic blood concentrations. Fortunately, no abnormalities have been reported in exposed infants.

Tacrolimus: Tacrolimus is generally not recommended in breastfeeding. However, there are two case reports suggesting minimal exposure to infants, due to a combination of low levels in breast milk and low oral bioavailability.

High-risk medications: There are limited data available on breast milk levels and infant serum levels of the above-listed high-risk medications. Many of these drugs are known teratogens with a strong possibility of accumulation in neonatal tissues and should therefore be avoided. For newer biologic agents, there are no published data available; until such data are reported, these agents should also be avoided.

In summary, many anti-inflammatory and immunosuppressive medications appear to be safe for use in lactating mothers. In each individual case, risks and benefits must be carefully weighed, and both mother and infant should be monitored for potential adverse effects. Available data suggest that disease control can often be optimized while simultaneously allowing both mother and infant to experience the numerous benefits of breastfeeding.

References
with CKD, high risk patients such as the elderly who are volume depleted and/or on concomitant diuretic therapy as well as in patients with asthma, since they may have aspirin-sensitive asthma that can cause fatal bronchospasm in susceptible individuals.

Concomitant use of NSAID’s and angiotensin converting enzyme inhibitor (ACE) inhibitors may lead to deterioration of renal function which is usually reversible. Therefore, the FDA recommends periodic monitoring of renal function in patients on this treatment combination. In order to reduce the risk of side effects due to NSAIDs, the FDA recommends using the lowest effective dose for the shortest possible duration.

Colchicine
Currently marketed in the USA as Colcrys, it was first marketed in combination with a uricosuric in 1939. In 2009, the FDA approved oral colchicine as a single therapy for acute gout. Thus, until recently there was no FDA- approved prescribing information, dosage or drug interaction warnings. Colchicine metabolism and excretion are mediated by P-glycoprotein (P-gp) and cytochrome P450 (CYP 3A4). Drugs that are potent inhibitors of P-gp such as cyclosporine and quinidine and CYP3A4 inhibitors such as clarithromycin, indinavir, itraconazole, ketoconazole, diltiazem, erythromycin, fluconazole, verapamil and grapefruit juice may increase colchicine levels and the risk of toxicity. The FDA recommends caution against concomitant use of P-gp or strong CYP3A4 inhibitors in patients with renal or hepatic impairment who are taking colchicine. In addition, the FDA suggests a dose reduction or interruption of colchicine treatment in patients who have been treated with a P-gp or CYP3A4 inhibitor within a 14 day period.

For patients with acute gout requiring repeated courses of colchicine consideration should be given to alternate therapy. For patients undergoing dialysis, the total recommended dose for the treatment of acute gout should be reduced to a single dose of 0.6 mg and the treatment course should not be repeated more than once every 2 weeks. Treatment of gout flares with colchicine is not recommended in patients with renal impairment receiving colchicine prophylaxis.

The most common adverse events due to colchicine use are gastrointestinal adverse events such as diarrhea, nausea and vomiting. Blood dyscrasias, neuromuscular toxicity and rhabdomyolysis have been reported especially in patients with CKD. Drug interactions with statins and fibrates have led to reports of rhabdomyolysis.

Corticosteroids
Side effects such as fluid retention, increased blood pressure, mood swings, weight gain, cataracts, hyperglycemia, increasing susceptibility to infections and osteoporosis are not uncommon. The FDA cautions against use of CS in patients with a recent myocardial infarction due to the risk of left ventricular free wall rupture and in patients with active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and ulcerative colitis, since CS increase the risk of a perforation.

ACTH
ACTH is contraindicated in patients with hypersensitivity to proteins of porcine origin, systemic fungal infections, ocular herpes simplex, recent surgery and history of peptic ulcer. Cost and limited availability make ACTH rarely used for gout.

IL – 1 inhibitors
Not approved by the FDA for gout. Off-label use may occur without regulatory approval by the FDA (especially Anakinra). Should not be given concurrently in patients on TNF-inhibitors.

Anakinra
The most common adverse reaction is infection site reaction (ISR) in up to 71% of patients which is the most common reason for discontinuation of therapy. The FDA warns about the increased risk of infection and since of patients in the Anakinra trials developed neutropenia, the FDA recommends baseline complete blood counts followed by monthly counts for 3 months, and quarterly for one year thereafter. Rates of malignancies were similar to that in the general population.

When prescribing drugs for gout one has to be mindful of the presence of comorbidities such as the metabolic syndrome, hypertension, dyslipidemia, cardiovascular disease, diabetes and chronic kidney disease (CKD) which are highly prevalent in gout patients.

URLATE LOWERING THERAPIES

Allopurinol
Most allopurinol skin rashes are mild. However, skin rashes can be the initial presentation of allopurinol hypersensitivity reactions including toxic epidermal necrolysis. Stevens Johnson syndrome and Allopurinol hypersensitivity syndrome (AHS) consisting of erythematous rash, fever, hepatitis acute renal failure and eosinophilia. This occurs in up to 0.3% of treated patients. Risk factors include female gender, age, chronic kidney disease, diuretic therapy and recently starting allopurinol. Prior to initiating allopurinol therapy a Polymerase Chain Reaction screen for HLA-B*5801 should be considered in Koreans with chronic kidney disease , Han Chinese or Thai descent as these populations are at increased risk for the AHS.

When concomitant use with azathioprine, 6 mercaptopurine and cyclosporine there is an increased risk of bone marrow suppression and therefore either drug can be dose reduced by 50% with close monitoring. Reduced doses are recommended in patients with hepatic insufficiency and in patients on dialysis, allopurinol should be dosed immediately after each dialysis treatment, since allopurinol and its metabolites are removed by dialysis.

Febuxostat
No dose adjustment is required for patients with mild or moderate renal impairment (GFR of 30-90 mL/min/1.73 m²). There is insufficient data in patients with severe renal impairment (GFR ≤30 mL/min/1.73 m²).

In the initial trials numerically there were more cardiovascular events documented in the febuxostat treated group as compared to the allopurinol group. A febuxostat versus allopurinol trial comparing cardiovascular outcomes is currently recruiting patients.

The FDA recommends getting baseline liver function tests before initiating febuxostat due to post-marketing reports of fatal and nonfatal hepatic failure. Concomitant therapy with azathioprine and 6 mercaptopurine led to an increased risk of bone marrow suppression and therefore is contraindicated. The FDA advises caution when using febuxostat with theophylline.

Probenecid
Caution should be used in patients with a history of renal calculi. In addition, patients with normal renal excretion of uric acid (overproducers) are at higher risk of developing renal lithiasis. Probenecid is contraindicated in patients with blood dyscrasias. Probenecid increases serum drug levels such as penicillin thus; we need to be mindful that high levels of other drugs have potential for toxicity. When used concomitantly with methotrexate (MTX) as well as other medications such as naproxen, rifampin and acetaminophen, the doses of the added medications such as MTX need to be lowered to prevent toxicity. Urinary alkalinization may be beneficial in patients with hematuria and renal colic to prevent the development of uric acid renal stones. Gastric intolerance is usually a sign that dosage should be reduced.

Pegloticase
Pegloticase is contraindicated in patients with Glucose-6-phosphate dehydrogenase (G-6PD) deficiency, hence, patients at high risk (African and Mediterranean ancestry) should be screened to prevent hemolysis and methemoglobinemia.
Some Safety Concerns for Drugs for Acute and Chronic Gout (continued from previous page)

In addition, oral ULT must be stopped before initiating pegloticase and should not be initiated while on pegloticase therapy. The FDA recommends caution using pegloticase in patients with congestive heart failure (CHF) due to CHF exacerbations observed during the clinical trials.

The most common adverse events are gout flares, infusion reactions (IRs), nausea, and anaphylaxis. Patients must be premedicated with antihistamines and corticosteroids due to the risk of infusion reactions and anaphylaxis. IRs include chest pain and discomfort, back pain, flushing, nausea and vomiting, erythema, muscle spasms, abdominal complaints, dyspnea, headaches, hyperhidrosis, change in blood pressure (increase or decrease), urticarial and pruritus. In trials all IRs resolved with supportive measures: slowing/ stopping infusion and/or antihistamines, fluids, CS, analgesics. Less common side effects are: contusion or ecchymosis, nasopharyngitis, constipation, chest pain, and vomiting. Most infusion reactions occurred after an increase in SU levels to more than 6 mg/dl. Thus, monitoring SU levels at baseline and prior to each infusion may help predict a heightened risk of infusion reactions. Treatment should be discontinued if levels increase to >6 mg/dl and especially over two consecutive times. D S Q

Safety signals

Vaccination is not a risk factor for SLE. Lamiae Grimaldi-Bensouda and colleagues asked 105 patients with recent onset SLE and 712 controls about receiving vaccinations. 21% of patients with SLE and 25% of the controls admitted receiving vaccinations and the difference if proportions was not statistically significant, leading the authors to conclude that routine vaccinations do not trigger SLE in the immediately following period. Grimaldi-Bensouda L, Le Guern V, Kone-Paut I, Aubrun E, Fain O, Ruel M, Machet L, Viallard JF, Magy-Bertrand N, Daugas E, Rossignol M, Abenhaim L, C costoL Calameau N; PGRx Lupus Study Group. The risk of systemic lupus erythematosus associated with vaccines: an international case-control study. Arthritis Rheumatol. 2014 Jun;66(6):1559-67. PMID: 24591123

Drug patch tests of limited value for identifying those at risk for severe cutaneous drug reactions. Toxidermies group of the French Society of Dermatopathology conducted a post hoc patch testing study of 135 patients who had developed serious cutaneous adverse drug reactions. They documented that the patch tests were positive for the putative offending drugs in no more than 68% of occasions, and that for most part the positivity was much lower. These indicate that a negative patch test cannot reliably exclude the risk for severe cutaneous drug reactions. Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, Grange A, Amarger S, Girardin P, Guin nepain MT, Tuchetet F, Lasek A, Waton J. Toxidermies group of the French Society of Dermatology. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. Br J Dermatol. 2013 Mar;168(3):555-62. PMID: 23136927

HLA-DR9, HLA-DR14 but not HLA-B8 is a risk factor for allopurinol hypersensitivity. The American college of Rheumatology guidelines to treat gout suggests that testing for HLA-B8 is useful for identifying those at risk for the allopurinol hypersensitivity. A new case control analysis of 463 cancer patients receiving allopurinol noted that maculopapular eruptions attributed to allopurinol were rare (3%) and where present were likely to be associated with HLA DR9 and DR14 types and not with B58. These data underlines the limitations of retrospective analyses for risk factors for allopurinol hypersensitivity. Jung JW, Kim JY, Yoon SS, Cho SH, Park SY, Kang HR. HLA-DR9 and DR14 Are Associated with the Allopurinol-Induced Hypersensitivity in Hematologic Malignancy. Tohoku J Exp Med. 2014;233(2):95-102. PMID: 24858023

Tofacitinib (Xeljanz) is associated with significant adverse reactions. In a recent report on the open label extension studies of 4102 patients with RA, the JAK inhibitor Tofacitinib was associated with serious adverse reactions in 15% patients and 21% had discontinued it. The number needed to harm was approximately 2 years for any adverse event and 30 years for serious infections. Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SF, Soma K, Nduaka CI, Benda B, Gruben D, Nakamura H, Komuro Y, Zwillich SH, Wang L, Riese RJ. Safety and Efficacy of Tofacitinib, an Oral Janus Kinase Inhibitor, for the Treatment of Rheumatoid Arthritis in Open-label, Longterm Extension Studies. J Rheumatol. 2014 May;41(5):837-52. doi: 10.3899/jrheum.130683. Epub 2014 Apr 1. PMID: 24692527

Rilanocept well tolerated in systemic Juvenile idiopathic arthritis (sJIA). In a 24 week randomized double blind trial 71 children with sJIA were equally randomized to placebo or rilanocept for 4 weeks. The placebo component lasted only 4 weeks. While there was no statistically significant increases in the incidence of serious infections, transaminitis, often more than twice the upper normal level was observed exclusively in the treatment group. The relatively short placebo phase makes it difficult to judge infection risks as well as longer term safety concerns. Ilowite NT, Prather K, Lokhnygina Y, Schanberg LE, Elder M, Milojevic D, Verbsky JW, Spalding SJ, Kimura Y, Imundo LF, Punaro MG, Sherry DD, Tarvin SE, Zemel LS, Birmingham JD, Gottlieb BS, Miller ML, O’Neil K, Ruth NM, Wallace CA, Singer NG, Sandborg CI. The randomized placebo phase study of rilanocept in the treatment of systemic juvenile idiopathic arthritis (RAPPORT). Arthritis Rheumatol. 2014 May 16. doi: 10.1002/art.38699. [Epub ahead of print] PMID: 24839206 D S Q
FDA MEDWATCH

FDA announces a procedural guidelines expedited drug approval program. In order to spur drug development in areas of unmet need and among those therapeutic areas where the new drug is expected to be substantially superior to the current state of treatment, the Agency proposes 4 separate, complementary administrative mechanisms: Priority Review, Accelerated Approval, Fast Track Designation, and breakthrough therapy designation. None of these will involve lowering the standards for approval or the quality of evidence needed.

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). Accelerated approval may be sought in trials where surrogate end points may be an acceptable alternative to clinical endpoints that may take a long time to document. A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

Revatio Caution: Revatio (sildenafil) has been approved to treat pulmonary artery hypertension among adults but have been utilized among children as well. The FDA cautions such use citing studies showing an increase in the risk for long term mortality associated with this drug.

Nexium is available over the counter. The FDA has approved NEXIUM 24HR (20 mg) for over-the-counter sale with 3 year market exclusivity to its manufacturer, Pfizer.

Safety Warning for Epidural injections. Based on the analysis of data from the FDA Adverse Event Reporting System (FAERS) and literature review, the Agency is warning that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death.

Lunesta dose reduction. Lunesta (eszopiclone) can cause next-day impairment of driving and other activities that require alertness Accordingly the FDA recommends reduction of Lunesta dose to 1 mg at bedtime.