Kidney disease: How should psoriasis patients with kidney failure / renal impairment be managed?

Narrative review of the existing literature was conducted.

Results/Answer:

A number of risk factors that predispose one to chronic kidney disease (CKD) are especially prevalent in people with multiple comorbidity including diabetes, hypertension, cardiovascular disease being treated with drugs that may impair kidney function. A UK population based study suggests that the risk of CKD stage 3-5 was slightly increased in people with psoriasis, independent of these risk factors [1]. Thus, the optimal choice of systemic therapy in the context of CKD is likely to be a relatively common clinical scenario. This is supported by data from the Spanish long-term pharmacovigilance registry indicating that 13 % of the total cohort were categorized as having "chronic renal failure" [2].

In a recent large-scale population-based study from Israel chronic renal failure occurrence was similar between psoriasis patients and the population control. In this study there was significantly less dialysis and kidney transplantation in the psoriasis group and more other kidney disease as compared to the control cohort. In pediatric patients there was no difference between psoriasis and the population for all kidney disorders [3].

Kidney diseases in psoriasis need to be seen in the context of other frequently associated disorders, in particular hypertension. It was shown that interleukin-17 can induce endothelial cell dysfunction and together with hypertension this may lead to renal injury. Salt intake was found as an aggravation factor [4].

Management of comorbidity is necessary to provide a holistic approach on psoriatic disease.

In people with established CKD, the following factors were considered when evaluating the treatment options for psoriasis:

- the likely effect of the psoriasis treatment on residual kidney function
- the impact of CKD on pharmacokinetics/pharmacodynamics of the psoriasis treatment
- potential drug interactions
- associated CKD co-morbidity

Systemic therapies

Acitretin

National guidelines in the UK [5], US [6] and Spain [7] all recommend avoiding acitretin in moderate-to-severe renal disease, although no evidence is cited underpinning these recommendations. There were no studies identified that specifically address the use of acitretin for psoriasis in the context of CKD. Acitretin is widely used in the renal transplant population for skin cancer prophylaxis where stage 3 CKD is common; a recent systematic review in this population showed no increased in AEs when compared to placebo [8]. Limited data from RCTs do not indicate that acitretin is a nephrotoxic drug. Acitretin is highly lipophilic, penetrates readily into body tissues and is highly protein (albumin) bound. Hypoalbuminemia in association with CKD may therefore potentially increase drug clearance. It is metabolized in the liver to 13-cis acitretin and etretinate, and then undergoes glucuronidation into inactive, water-soluble forms. In healthy patients, acitretin is excreted entirely in the form of these inactive metabolites, in approximately equal parts via the kidneys and the bile. In a single report [9], the mean areas under the plasma concentration versus time curves of acitretin and 13-cis acitretin following a single oral dose of 50 mg of acitretin in six patients on hemodialysis were, in fact, about 50 % lower than healthy controls. No retinoids were detectable in the dialysate.

In summary, acitretin is not known to be nephrotoxic, and CKD (any stage) would not be predicted to markedly impact on drug disposition.

Apremilast

Apremilast has no known nephrotoxic potential. In the pivotal clinical trials there was no evidence for treatment emergent adverse events related to renal function[10,11].

In patients with mild to moderate impairment of kidney function, no dose adjustment of apremilast is necessary. When patients have severe impairment of kidney function (eGFR below 30 ml/min/1,73 m2 or CLcr < 30 ml/min) the dose of apremilast should be reduced to 30 mg once daily. When starting treatment with apremilast in case of severe renal insufficiency only the morning dose should be given as total daily dose (recommendations according to SmPC).

Fumarates

Fumarates are known to be potentially nephrotoxic, and may rarely cause an irreversible, proximal renal tubular nephropathy with long-term use. Recent studies [12] of dimethyl fumarate (for MS) confirm proteinuria and reduction in eGFR to occur more commonly than placebo; German guidelines and the SmPC specify careful monitoring of serum creatinine, and treatment cessation in the event of

significant change. In health, fumarates are extensively metabolised by ubiquitous esterases, and so CKD would not be predicted to significantly impact on drug clearance [13,14].

Ciclosporin

Ciclosporin has established nephrotoxic potential. Acute nephrotoxicity can occur within weeks of treatment initiation, is reversible, and arises due to dose-dependent vascular dysfunction, involving afferent arteriolar constriction that leads to increased vascular resistance and a decrease in glomerular filtration rate. Tubular dysfunction may also occur, characterized by decreased magnesium re-absorption, decreased uric acid excretion, decreased potassium and hydrogen ion secretion, and distal tubular acidosis. Chronic nephrotoxicity [15,16] is largely irreversible and is characterized by progressive arteriolar hyalinosis, interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Chronic nephrotoxicity is more likely to occur with higher daily doses, larger cumulative doses and long-term therapy (more than 1-2 years). In one long-term psoriasis study, patients with a pre-treatment creatinine of > 100 µmol/L were more likely to discontinue therapy.. In a study performed in patients with (stage 5) terminal renal failure, the systemic clearance was approximately two thirds of that in patients with normally functioning kidneys. Less than 1 % of the administered dose is removed by dialysis.

Guidelines recommend using CsA with caution in people with CKD; in those with significant reduction in renal function (CKD stage 3 or more) [17], CsA nephrotoxicity may lead to further critical reduction in function.

Methotrexate

MTX is not generally considered nephrotoxic when used at low doses for inflammatory disease, although renal impairment is reported [18], and may be an under-recognized event. MTX and 7-hydroxymethotrexate are mainly excreted through the kidneys, via glomerular filtration and active transport. Methotrexate clearance is therefore reduced (and thus risk of toxicity increased) in the context of CKD, depending on the stage. In a cohort of 77 patients with RA and various stages of CKD, the elimination half-life of a single dose of intramuscular MTX (7.5-15 mg) was directly related to GFR, with a decrease in MTX of 44.7 % in the category of patients with the poorest renal function (i. e., creatinine clearance < 45 ml/min, roughly equivalent to stage 3b) [19]. Pooling data from RCTs of MTX for RA also indicates that presence of renal impairment (creatinine clearance < 79 ml/min) increases the OR for severe and pulmonary toxicity by four compared to those with a creatinine clearance > 99.8 ml/min (reference group) [20]. There are no studies evaluating use of MTX for psoriasis with CKD.

US guidelines [6] consider renal impairment a relative contra-indication to MTX, and all recent RCTs with a MTX arm exclude patients with 'significant' renal impairment. There are several case reports of life threatening toxicity following MTX use in people on dialysis (reviewed in [21]). Guidelines in the rheumatology literature, largely consequent on the two studies referenced above, recommend avoiding MTX in people with creatinine clearance of < 20 ml/min, and halving the dose in those between 20 and 50 ml/min (summarized in [22]).

Biological therapy

To date, nephrotoxicity has not been reported as an AE in relation to all groups of biologic agents (TNFi, IL-17A/IL-17RA antagonists, IL-12/23p40 antagonists, and IL-23p19 antagonists. Clearance of biological therapies should not be affected in case of CKD (of any stage).

We **recommend** ensuring an accurate assessment of renal function in any psoriasis patient with known or suspected chronic kidney disease prior to therapy.	↑↑	STRONG CONSENSUS[1] 100 % Agreement EXPERT CONSENSUS
We **recommend** working in collaboration with the nephrologist when prescribing systemic therapy in any psoriasis patient with chronic kidney disease of stage 3 (eGFR <60 mL/min/1.73 m²) or more.	↑↑	
We **suggest** acitretin*, apremilast, fumarates*, methotrexate* **may be used** in psoriasis patients with **mild to moderate renal impairment** (eGFR ≥30 mL/min/1.73m²). *(carefull dosing/dose adjustment may be needed)	↑	
We **suggest** using biologics in psoriasis patients with chronic kidney disease and all stages of renal impairment.	↑	
We **recommend against** using ciclosporin, fumarates, or methotrexate in psoriasis patients with **chronic kidney disease and severe renal** impairment (eGFR <30 mL/min/1.73m²).	↓↓	

[1] due to personal-financial conflict of interest 3 abstentions

References

1. Schonmann Y, Mansfield KE, Mulick A, et al. Inflammatory skin diseases and the risk of chronic kidney disease: population-based case-control and cohort analyses. *The British journal of dermatology*. Oct 2021;185(4):772-780. doi:10.1111/bjd.20067
2. Garcia-Doval I, Carretero G, Vanaclocha F, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. *Archives of dermatology*. Apr 2012;148(4):463-70. doi:10.1001/archdermatol.2011.2768
3. Friedland R, Kridin K, Cohen AD, Landau D, Ben-Amitai D. Psoriasis and Renal Disorders: A Large-Scale Population-Based Study in Children and Adults. *Dermatology*. 2022;238(5):904-909. doi:10.1159/000522228
4. Higaki A, Mahmoud AUM, Paradis P, Schiffrin EL. Role of interleukin-23/interleukin-17 axis in T-cell-mediated actions in hypertension. *Cardiovasc Res*. Apr 23 2021;117(5):1274-1283. doi:10.1093/cvr/cvaa257
5. Ormerod AD, Campalani E, Goodfield MJ, Unit BADCS. British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. *The British journal of dermatology*. May 2010;162(5):952-63. doi:10.1111/j.1365-2133.2010.09755.x
6. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. Sep 2009;61(3):451-85. doi:10.1016/j.jaad.2009.03.027
7. Carretero G, Ribera M, Belinchon I, et al. Guidelines for the use of acitretin in psoriasis. Psoriasis Group of the Spanish Academy of Dermatology and Venereology. *Actas dermo-sifiliograficas*. Sep 2013;104(7):598-616. doi:10.1016/j.adengl.2013.01.001
8. Bath-Hextall F, Leonardi-Bee J, Somchand N, Webster A, Delitt J, Perkins W. Interventions for preventing non-melanoma skin cancers in high-risk groups. *The Cochrane database of systematic reviews*. 2007;4(4):CD005414. doi:10.1002/14651858.CD005414.pub2
9. Stuck AE, Brindley CJ, Busslinger A, Frey FJ. Pharmacokinetics of acitretin and its 13-cis metabolite in patients on haemodialysis. *British journal of clinical pharmacology*. Mar 1989;27(3):301-4.
10. Chimenti MS, Gramiccia T, Saraceno R, et al. Apremilast for the treatment of psoriasis. *Expert opinion on pharmacotherapy*. 2015;16(13):2083-94. doi:10.1517/14656566.2015.1076794
11. European Medicines Agency. Otezla SmPC and Patient Leaflet. The electronic medicines compendium. https://www.medicines.org.uk/emc/product/10709/smpc
12. Cada DJ, Levien TL, Baker DE. Dimethyl fumarate. *Hospital pharmacy*. Sep 2013;48(8):668-79. doi:10.1310/hpj4808-668
13. Rostami-Yazdi M, Clement B, Mrowietz U. Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients. *Archives of dermatological research*. Sep 2010;302(7):531-8. doi:10.1007/s00403-010-1061-4
14. Rostami-Yazdi M, Clement B, Schmidt TJ, Schinor D, Mrowietz U. Detection of metabolites of fumaric acid esters in human urine: implications for their mode of action. *The Journal of investigative dermatology*. Jan 2009;129(1):231-4. doi:10.1038/jid.2008.197
15. Maza A, Montaudie H, Sbidian E, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV*. May 2011;25 Suppl 2:19-27. doi:10.1111/j.1468-3083.2011.03992.x
16. Issa N, Kukla A, Ibrahim HN. Calcineurin inhibitor nephrotoxicity: a review and perspective of the evidence. *American journal of nephrology*. 2013;37(6):602-12. doi:10.1159/000351648

17. Chadban SJ, Barraclough KA, Campbell SB, et al. KHA-CARI guideline: KHA-CARI adaptation of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Nephrology*. Mar 2012;17(3):204-14. doi:10.1111/j.1440-1797.2011.01559.x
18. Kremer JM, Petrillo GF, Hamilton RA. Pharmacokinetics and renal function in patients with rheumatoid arthritis receiving a standard dose of oral weekly methotrexate: association with significant decreases in creatinine clearance and renal clearance of the drug after 6 months of therapy. *J Rheumatol*. Jan 1995;22(1):38-40.
19. Bressolle F, Bologna C, Kinowski JM, Sany J, Combe B. Effects of moderate renal insufficiency on pharmacokinetics of methotrexate in rheumatoid arthritis patients. *Annals of the rheumatic diseases*. Feb 1998;57(2):110-3. doi:10.1136/ard.57.2.110
20. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. *J Rheumatol*. Feb 1995;22(2):218-23.
21. Willner N, Storch S, Tadmor T, Schiff E. Almost a tragedy: severe methotrexate toxicity in a hemodialysis patient treated for ectopic pregnancy. *European journal of clinical pharmacology*. Mar 2014;70(3):261-3. doi:10.1007/s00228-013-1608-3
22. Le Boedec M, Marhadour T, Devauchelle-Pensec V, et al. Baseline laboratory test abnormalities are common in early arthritis but rarely contraindicate methotrexate: study of three cohorts (ESPOIR, VErA, and Brittany). *Seminars in arthritis and rheumatism*. Apr 2013;42(5):474-81. doi:10.1016/j.semarthrit.2012.08.001