



## 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 was increased in people with moderate-to-severe psoriasis, independent of these risk factors <sup>1</sup>. 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” <sup>2</sup>.

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 <sup>3</sup>, US <sup>4</sup> and Spain <sup>5</sup> 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 <sup>6</sup>. 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 <sup>7</sup>, 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<sup>8,9</sup>.

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 m<sup>2</sup> 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<sup>10</sup> 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<sup>11,12</sup>.

### **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<sup>13,14</sup> 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) <sup>15</sup>, 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 <sup>16</sup>, 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) <sup>17</sup>. 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) <sup>18</sup>. There are no studies evaluating use of MTX for psoriasis with CKD. US guidelines <sup>4</sup> 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 <sup>19</sup>). 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 <sup>20</sup>).

### **Biological therapy**

To date, nephrotoxicity has not been reported as an AE in relation to all groups of biologic agents (TNF antagonists, 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).



<p>We <b>recommend</b> ensuring an accurate assessment of renal function in any psoriasis patient with known or suspected chronic kidney disease prior to therapy.</p>	↑↑	
<p>We <b>recommend</b> working in collaboration with the nephrologist when prescribing systemic therapy in any psoriasis patient with chronic kidney disease of stage 3 (eGFR &lt;60 mL/min/1.73 m<sup>2</sup>) or more.</p>	↑↑	
<p>We <b>suggest</b> acitretin*, apremilast, fumarates*, methotrexate* <b>may be used</b> in psoriasis patients with <b>mild to moderate renal impairment</b> (eGFR ≥30 mL/min/1.73m<sup>2</sup>).</p> <p>*(carefull dosing/dose adjustment may be needed)</p>	↑	<p>STRONG CONSENSUS<sup>1</sup></p>  <p>EXPERT CONSENSUS</p>
<p>We <b>suggest</b> using biologics in psoriasis patients with chronic kidney disease and all stages of renal impairment.</p>	↑	
<p>We <b>recommend against</b> using ciclosporin, fumarates, or methotrexate in psoriasis patients with <b>chronic kidney disease and severe renal impairment</b> (eGFR &lt;30 mL/min/1.73m<sup>2</sup>).</p>	↓↓	

<sup>1</sup> due to personal-financial conflict of interest 3 abstentions



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