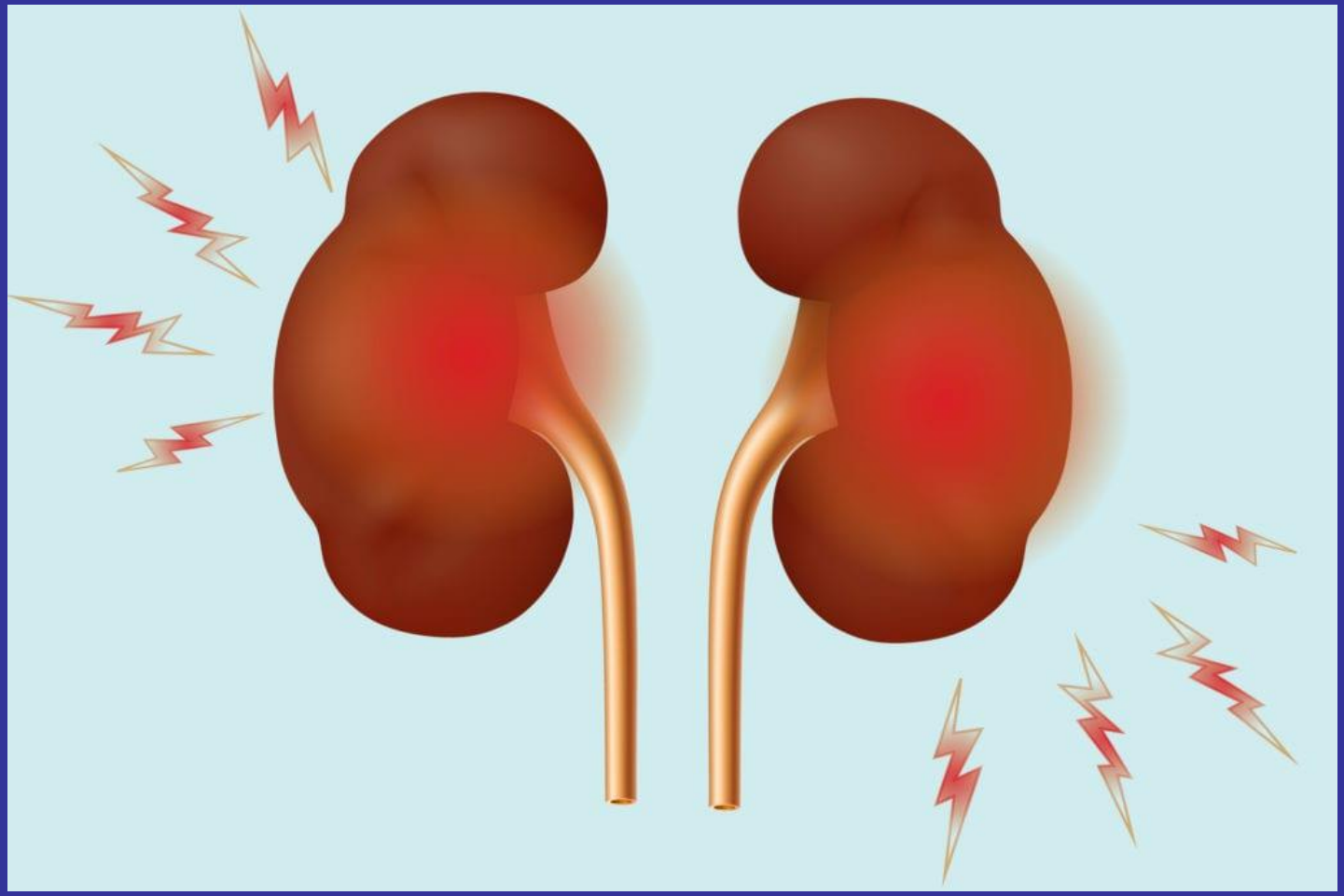
IN THE NAME OF GOD

Management of Rheumatoid arthritis in kidney disease



kidney disease in rheumatoid arthritis

- Kidney disease appeared in patients with RA most often during the first 10–15 years of RA disease.
- A significant percentage of patients with RA without baseline nephropathy progressed to CKD over time.
- The reported prevalence of kidney disease in patients with RA ranges from 5–50%, reflecting wide variations in the diagnostic criteria and definitions of renal disease, and different study designs .
- In a cross-sectional population-based cohort study of 604 Finnish patients with RA, 17% had evidence of nephropathy (defined as hematuria, proteinuria, or kidney failure)

Chronic kidney disease in rheumatoid arthritis

- A total of cohort studies (three retrospective cohort studies and four prospective cohort study) comprising of 1,627,833 participants met the inclusion criteria and were included in the meta-analysis.
- The overall quality of the included studies was good.
- The risk of incident CKD was significantly increased among patients with RA with the pooled risk ratio of 1.52 (95% CI 1.28–1.80).
- The incidence of CKD increases over time among RA patients and prevalent CKD may be an insidious risk factor linked to increased mortality in RA patients.

Chronic kidney disease in rheumatoid arthritis

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- The development of CKD in patients with RA is multifactorial and may result from several ongoing processes, including primary or secondary renal involvement associated with RA (eg, GN), chronic inflammation, comorbidities(High blood pressure diabetes, hyperlipidemia(High cholesterol) .CV disease Obesity)High-salt diet and nephrotoxic anti rheumatic drugs..

- Physicians should monitor the renal function of patients with RA regularly and intervene to tightly control CV risk factors and the progression of CKD, particularly in patients who are older, NSAID users, or have comorbidities.

Chronic kidney disease in rheumatoid arthritis

- Renal involvement can be caused by drugs for RA.
- Patients with RA need often long term therapy with the drugs that are associated with nephrotoxicity such as NSAIDs and DMARDs.
- Chronic use of NSAIDs is associated with declining eGFR in RA patients.
- In DMARDs, gold, penicillamine or bucillamine can be associated with proteinuria.
- Calcineurin inhibitors, such as cyclosporine and tacrolimus, can induce declining GFR.
- Glucocorticoids, mycophenolate mofetil and cyclophosphamide were associated with increased risk of CKD might be because prescription of these drugs indicates higher disease activity or presence of comorbidity, resulting in rapidly declining renal function.
- There are also multiple reports of glomerulonephritis associated with anti-tumor necrosis factor alpha therapy in patients with RA,t hese include proliferative lupus nephritis, pauci-immune crescentic glomerulonephritis, and membranous nephropathy .

The Role of Rheumatologists in the Management of KD Patients

- A team approach involving rheumatologists and nephrologists is expected to produce a complementary effect and achieve better outcomes .

- First, rheumatologists should investigate extra-renal manifestations on physical examination suggestive of RA relapse
- Second, rheumatologists should assess activity of RAs and the need for adjusting treatment. Physical examination on a regular basis is pertinent because serologic parameters may not serve as accurate markers of disease activity and may not help predict disease recurrence in patients with ESRD.

- Third, rheumatologists should adjust the doses of those of immunosuppressive agents such as hydroxychloroquine,and CYC, if necessary.
- Although the activity of most RA tends to decrease after initiation of hemodialysis, disease activity may still increase, and recognizing how to appropriately use immunosuppressive agents even after the development of ESRD is crucial .

Management of ESRD and RA Patients

- The literature contains little information on the treatment of RA in patients with end-stage renal failure who are on haemodialysis.
- The potential toxicity of the drugs used, such as NSAIDs and disease-modifying drugs, deserves special attention.
- NSAIDs expose dialysis patients to an increased risk of gastroduodenal ulceration and bleeding, and it is advised that their use should be limited to short courses

Management of ESRD and RA Patients

- About 90% of the absorbed MTX is excreted in the urine unchanged within 48 h by glomerular filtration and tubular secretion.

- Methotrexate, is cleared primarily by the kidney and has been associated with life-threatening complications in a patient on haemodialysis who was on a small dose .

- The nephrotoxicity of high-dose MTX are well recognized, the role of the low-dose MTX used in RA is not clear.

MTX

- This dose can be increased by steps of 2.5–5.0 mg, up to a maximal dose of 25 mg/week.
- The elimination half-life of MTX increases (for instance, 120 h in a peritoneal dialysis patient ,as compared with 8 h in normal RF patients) and the total clearance decreases with the degree of renal impairment
- The use of MTX even at very low doses (2.5 mg once a week) and after a single administration in patients with a GFR <15 ml/min/1.73 m^2 may have severe or even fatal consequences MTX prescription is thus not recommended in patients with a GFR <15 ml/min/1.73 m^2 .
- In patients with stages 3 and 4 KD (GFR between 15 and 60 ml/min/1.73 m^2), the initial dose range is 2.5–7.5 mg/week, which then may be increased up to a maximal dose of 12.5 mg/week (50% of the dose normally used) . MTX is contraindicated in ESRD patients because it causes severe bone marrow suppression and neutropenia.

Methotrexate-related toxicity in patients with rheumatoid arthritis and renal dysfunction

- This study aimed to investigate methotrexate (MTX)-related toxicity in patients with rheumatoid arthritis (RA) and renal dysfunction.
- This retrospective cohort study included patients with RA and renal dysfunction.
- The study included 120 patients with RA and renal dysfunction receiving MTX (66: newly developed; 54: previously developed). The median eGFR was 52.1 mL/min/1.73 m2 [IQR 47.1–57.3].
- Thirty-five patients (29.2%) experienced toxicity, and the median time to toxicity events was 23 months (IQR 10–57)

Methotrexate-related toxicity in patients with rheumatoid arthritis and renal dysfunction

- Multivariate analysis revealed that hydroxychloroquine use (HR 0.425, 95% CI 0.212–0.853, $P = 0.016$), baseline eGFR (HR 0.938, 95% CI 0.890–0.988, $P = 0.015$) and being female (HR 10.538, 95% CI 1.375–80.793, $P = 0.023$) were associated with MTX-related toxicity.

- Toxicity occurred in approximately 30% of patients with RA and renal dysfunction receiving MTX treatment.

- Hydroxychloroquine use exhibited a protective effect against MTX-associated toxicity development

Hydroxychloroquine

- The hydroxychloroquine dose should be reduced by 50% in renal impairment.
- Renal failure predisposes to a higher incidence of myopathy, neuropathy and cardiac myotoxicity in patients on hydroxychloroquine .
- Patients with renal disease may have unpredictably high blood drug levels because hydroxychloroquine is eliminated to a large degree through the kidney.
- Hydroxychloroquine-associated retinal toxicity may be increased in ESRD patients, and both dosage and monitoring frequency need to be adjusted . Hydroxychloroquine use
- In patients with newly diagnosed rheumatoid arthritis is associated with a significantly lower risk of incident CKD compared with in nonusers.

Management of ESRD and RA Patients

- It is important to note that most immunosuppressive agents, except for azathioprine and CYC, show no intr adialytic clearance with hemodialysis .
- Although safety data are limited, several immunosuppressive agents appear to be useful for reducing corticosteroid use and improving extra-renal manifestations of RA in ESRD.

CYC

- ESRD patients have reduced systemic clearance of CYC with a prolonged elimination half-life, and IVCY dose adjustment may be required for patients with high serum creatinine levels.
- In hemodialysis patients, on average, 22% of the administered CYC dose was eliminated by a three-hour hemodialysis session starting 7 hours after CYC administration.
- Thus, IV CYC should be administered after dialysis

CSA and TAC

- These agents undergo minimal renal elimination and their mean clearance in patients with ESRD was similar to that in patients with normal renal function.

- However, careful monitoring of eGFR is recommended to predict nephrotoxicity.
- Dose reduction is necessary whenever serum creatinine increases by more than 30%

- Dose adjustment CSA should be performed when a trough concentration is higher than 200 ng/mL to prevent nephrotoxicity .
- Appropriate therapeutic drug monitoring is useful for optimizing TAC doses when the trough concentration is higher than 20 ng/mL.
- Cyclosporin may be given to patients with renal impairment on haemodialysis, at the same dose for patients with normal renal function .

Other disease-modifying antirheumatic drugs

- Sulfasalazine has also been reported to be safe in RA patients with ESRD after titration to full therapeutic doses.

- Leflunomide can be used in patients with ESRD without significant dose reduction due to the stable concentration of its active metabolite, teriflunomide, which is only partially removed by dialysis

Treatment of rheumatoid arthritis with biologic agents lowers the risk of incident chronic kidney disease

- However, little is known about the effects of using the newer novel non-nephrotoxic biologic agents on the risk of incident CKD.
- To study this we used a cohort of 20,757 United States veterans diagnosed with rheumatoid arthritis with an estimated (eGFR) of 60 mL/min/1.73m^2 or more, recruited between October 2004 and September 2006, and followed through 2013.

Treatment of rheumatoid arthritis with biologic agents lowers the risk of incident chronic kidney disease

- The associations of biologic use with incident CKD (eGFR under 60 with a decrease of at least 25% from baseline, and eGFR under 45 mL/min/1.73m^2) and change in eGFR (<-3, -3 to <0 [reference], and ≥0 mL/min/1.73m^2/year) were examined in propensity-matched patients based on their likelihood to initiate biologic treatment.
- Thus, biologic agent administration was independently associated with lower risk of incident CKD and progressive eGFR decline

Renal disease in patients with rheumatoid arthritis treated with biological therapy

- ABSTRACT:

✓ The use of biological therapies may have positive impact on chronic renal disease associated with rheumatoid arthritis.

✓ The study evaluates retrospectively renal function in 57patients with rheumatoid arthritis treated with differenttypes of biological therapy, comparative with 62 RApatients treated conservatively with DMARDs.Patients treated with biological therapies presented a lower mean value for serum creatinine measured bothat baseline and after 6 months of treatment, statisticallysignificant compared with the subgroup treated withDMARDs (0.69 ± 0.17 mg/dL vs. 1.18 ± 1.01 mg/dL,p = 0.003).

✓ Results for estimated filtration rate were significantly increased in biologically treated cohort (100.36 ± 16.76 mL/min/1.73 m2 vs. 63.49 ± 21.60 mL/min/1.73 m2, p < 0.00001).

✓ Rituximab presenteda better estimated filtration rate compared with other biological tharapies (eGFR 97.037 mL/min/1.73 m2 vs. 90.933 mL/min/1.73 m2).

✓ The positive effect of potent biological anti-inflammatorytherapies sustains the need of further exploring therisk of reduced kidney function in immune-mediated diseases, including rheumatoid arthritis.

Anti TNF-α

- Anti TNF-α is a new category of drug used in the treatment of RA, but very little is known about its use in renal impairment or in haemodialysis
- That patients on haemodialysis can tolerate this drug and that the drug maintains its efficacy

Etanercept treatment in rheumatoid arthritis patients with chronic kidney failure on predialysis

- All three patients improved after starting etanercept treatment and their steroid requirements were decreased.

- Linear relationships between Modification of Diet in Renal Disease study equation (MDRD) glomerular filtration rate (GFR) and time were observed. Thus, in all patients, the changes in GFR did not represent superimposed acute drug toxicity, but rather chronic progressive renal failure.

- These cases show that etanercept may be a safe and effective treatment option for RA patients with chronic kidney failure.

Effect of anti-tumor necrosis factor alpha treatment of rheumatoid arthritis and chronic kidney disease

- Seventy patients with RA and CKD were retrospectively analyzed. Outcomes were evaluated using the difference in the annual change of estimated glomerular filtration rate (eGFR) between patients treated with anti-TNF-α or without.
- The annual change of eGFR was significantly different between patients treated with anti-TNF-α drugs and without (2.0 ± 7.0 ml/min/1.73 m^2/year vs. -1.9 ± 4.0 ml/min/1.73 m^2/year; difference in mean vs. -3.9 ± 7.3 ml/min/1.73 m^2/year; $p = 0.006$).
- Use of anti-TNF-α drugs was significantly associated with positive annual change of eGFR in multivariate logistic regression analysis ($p = 0.019$).
- Among patients with RA and CKD, treatment with anti-TNF-α drugs was associated with less renal function decline.
- Anti-TNF-α drugs may be beneficial for managing RA combined with CKD.

Effectiveness and safety of tocilizumabtherapy for patients with rheumatoid arthritis and renal insufficiency: a real-life registrystudy in Japan (the ACTRA-RI study)

- The ACTRA-RI (Actemra for RA patients with renal insufficiency)study was designed to evaluate the efficacy and safety of tocilizumab (TCZ) therapy in the real-life registry of patientswith RA and renal insufficiency.
- For this study, we registered all patients with RA who had begun TCZ therapy in participating hospitals as of January 2014 (total 405 patients with RA)

- 102 with renal insufficiency and 303 without). In this multicentre study, the 24-week TCZ therapy had good efficacy parameters as well as stable safety and tolerability profiles in patients with RA and renal insufficiency, regardless of MTX use.

Recommended Dosages of Immunosuppressive Agent in Patients with ESRD

Agent	Recommended dosage
Hydroxychloroquine	Both dosage and screening frequency need to be adjusted
Mycophenolate mofetil	TDM is recommended. The target MPA-AUC (0-12 h) concentration in rheumatic disease is controversial ,**Contraindicated**
Cyclophosphamide	with high serum Cr and/or old age. Intravenous CYC infusions 15 mg/kg/pulse in patients <60 years with low Cr (150–300 μmol/L or 1.7–3.4 mg/dL). 12.5 mg/kg/pulse in patients with 60–70 years and low Cr. 10.0 mg/kg/pulse in patients >70 years with low Cr. 12.5 mg/kg/pulse in patients <60 years with high Cr (300–500 μmol/L or 1.7–3.4 mg/dL). 10.0 mg/kg/pulse in patients with 60–70 years and high Cr. 7.5 mg/kg/pulse in patients >70 years with low Cr.
Cyclosporine	TDM is recommended. Trough concentration should not exceed 200 ng/mL.

Recommended Dosages of Immunosuppressive Agent in Patients with ESRD

Agent	Recommended dosage
Tacrolimus	**TDM is recommended. Trough concentration should not exceed 20 ng/mL.**
Azathioprine	**CCr > 50 mL/minute, no dose adjustment recommended; CCr 10–50 mL/minute, 75% of normal dose; CCr < 10 mL/minute, 50% of normal dose Patients on hemodialysis (–45% removed in 8 hours by dialysis): 50% of normal dose for children; for adults, 50% of normal dose and supplement of 0.25 mg/kg after hemodialysis on dialysis days**
Methotrexate	**Contraindicated**
Leflunomide	**Dose adjustment is not required**
Sulfasalazine	**Dose adjustment is not required**

Recommended Dosages of Immunosuppressive Agent in Patients with ESRD

Agent	Recommended dosage
Iguratimod	Careful administration is required
Bucillamine	Contraindicated
Belimumab	Dose adjustment is not required
Rituximab	Dose adjustment is not required

Conclusion

- Prevalence of KD indicators in RA patients is common.
- Chronic kidney involvement in patients with rheumatoid arthritis seems to be more a result of chronic inflammatory status, an entity apart of pharmacological drug effect on renal function or amiloidosis
- Nearly half of the RA patients are presenting a KD according to NKF classification.
- Systematic estimation of GFR with CG or aMDRD formula even at levels of SCr usually considered as ‘normal’ and assessment of urine dipstick is necessary in RA patients.
- In patients with KD at high risk for drug toxicity, dosage should be adapted to RF and the use of nephrotoxic therapies should be avoided whenever possible.

CONCLUSION

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- Furthermore, using potentially nephrotoxic drugs will also require specific monitoring and, when available, specific prevention methods to help reduce the risk for renal toxicity, especially in patients with already abnormal RF.
- However, statins should be considered in patients who have multiple risk factors for cardiovascular disease, because the incidence of cardiovascular disease in patients with RA is higher than in the control population .
- Management and control of systemic inflammation associated with RA.
- Regular monitoring of renal function should be implemented, especially for elderly RA patients with hypertension.
- Identification of the high-risk group for renal dysfunction can not only facilitate early intervention to prevent this complication but can also help to achieve optimal management of RA patients

References

1. KeiichiSumida,Treatment of rheumatoid arthritis with biologic agents lowers the risk of incident chronic kidney disease,Kidney International, May (2018)
2. Shunsuke Mori, ,Prevalence of and factors associated with renal dysfunction in rheumatoid arthritis patients: a cross-sectional study in community hospitals *Clinical Rheumatology* (2017)
3. Hans-Joachim Anders , Renal co-morbidity in patients with rheumatic diseases *Arthritis Research & Therapy* , (2011)
4. Takeshi Tokoroyama ,Prevalence, incidence and prognosis of chronic kidney disease classified according to current guidelines: a large retrospective cohort study of rheumatoid arthritis patients , *Nephrology Dialysis Transplantation*, (2019)
5. Sukit Raksasuk ,Patients with rheumatoid arthritis have an increased risk of incident chronic kidney disease: a systematic review and meta-analysis of cohort studies & Patompong Ungprasert . *International Urology and Nephrology* , (2020)
6. Shunsuke Mori, Prevalence of and factors associated with renal dysfunction in rheumatoid arthritis patients: a cross-sectional study in community hospitals Clin Rheumatol (2017)
7. Soo-Kyung Cho Etanercept treatment in rheumatoid arthritis patients with chronic kidney failure on predialysis *Rheumatology International,(*2010)
8. Nephrol Dial Transplant 2005

References

9. Hsien-Yi ChiuIncreased Risk of Chronic Kidney Disease in Rheumatoid Arthritis Associated with Cardiovascular Complications – A National Population-Based Cohort Study,POLS,(2015)
10. Koichiro Saisho , Prevalence of chronic kidney disease and administration of RA-related drugs in patients with RA: The NinJa 2012 study in Japan, Mar 2016.
11. Hyun Woo Kim, Effect of anti-tumor necrosis factor alpha treatment of rheumatoid arthritis and chronic kidney disease, Rheumatology international *Rheumatology*, March 2006.
12. Hammoudeh Infliximab treatment in a patient with rheumatoid arthritis on haemodialysis *Rheumatology*,, March 2006 Hyun Woo Kim, Effect of anti-tumor necrosis factor alpha treatment of rheumatoid arthritis and chronic kidney disease, Rheumatology international *Rheumatology*, March 2006 M.
13. Hammoudeh Infliximab treatment in a patient with rheumatoid arthritis on haemodialysis *Rheumatology*,, March 2006
14. Effectiveness and safety of tocilizumab therapy for patients with rheumatoid arthritis and renal insufficiency: a real-life registry study in Japan (the ACTRA-RI study) Ann Rheum Dis March 2015
15. Miklos Z.Molnar. Treatment of rheumatoid arthritis with biologic agents lowers the risk of incident chronic kidney disease/j.kint.2017