TREATMENT OF REFRACTORY LUPUS NEPHRITIS

ST. FAEZI

ASSOSCIATE PROFESSOR OF RHEUMATOLOGY

TEHRAN UNIVERSITY OF MEDICAL SCIENCES (TUMS)

- Lupus nephritis is the most common organ-threatening manifestation of systemic lupus erythematosus (SLE) and continues to result in significant morbidity and mortality.

- Maria Dall'Era. **Curr Opin Rheumatol** 2017

- Unfortunately, a subset of LN patients fails to respond to immunosuppression remain refractory and are a management challenge with a high risk of a poor outcome.

- The true prevalence is not known
- It has been estimated to be between 14% - 33%.

- Moroni G, et al. *Expert Rev Clin Immunol*. 2015

Definition

- There is no consensus definition of “refractory” LN, but the term implies an inadequate or no response to the remission-inducing treatment.

TABLE 59.6 Renal Response Criteria

American College of Rheumatology Guidelines[a] 2006[171]	
Complete response	eGFR >90 mL/min/m²
	Proteinuria ≤0.2 g/g
	Inactive urinary sediment (<5 RBC/HPF,<5 WBC/HPF, no cellular casts)
Partial response	Normal or stable renal function
	Proteinuria 0.2–2.0 g/g with at least 50% reduction from baseline
	Inactive urinary sediment
Spanish (S.E.N.) Guidelines 2012[121]	
Complete response	Serum creatinine <1.2 mg/dL (or decrease to initial values or ±15% of baseline value in patients with creatinine >1.2)
	Proteinuria ≤0.5 g/day
	Inactive urinary sediment (≤5 RBC/HPF, ≤5 WBC/HPF, no RBC casts)
	Serum albumin >3 g/dL
Partial response	In patients with proteinuria ≥3.5 g/day, decrease to <3.5 g/day.
	In patients with proteinuria <3.5 g/day, >50% reduction in proteinuria compared with initial values
	Stabilization (±25%) or improvement in serum creatinine
KDIGO Guidelines 2012[21]	
Complete response	Return of serum creatinine to previous baseline
	Decline in UPCR (from a 24-hour urine collection) to <500 mg/g (<50 mg/mmol)
Partial response	Stabilization (±25%), or improvement of serum creatinine, but not to normal
	≥50% decrease in UPCR (from a 24-hour urine collection)
	If proteinuria was nephrotic range, improvement requires a IPCR <3000 mg/day
EULAR/EDTA[a] 2012[120]	
Complete response	Proteinuria <50 mg/mmol per day (approximately <0.5 g/day)
	Normal or near-normal (within 10% of normal GFR if previously abnormal) renal function
Partial response	Proteinuria reduction by ≥50% and to subnephrotic levels
	Normal or near-normal GFR

- The EULAR/ERA-EDTA guidelines define refractory disease as:
  - Failure to improve within 3–4 months
  - Not achieving partial response after 6–12 months
  - Not achieving complete response after 2 years of treatment

EULAR/EDTA[a] 2012[120]	
Complete response	Proteinuria <50 mg/mmol per day (approximately <0.5 g/day) Normal or near-normal (within 10% of normal GFR if previously abnormal) renal function
Partial response	Proteinuria reduction by ≥50% and to subnephrotic levels Normal or near-normal GFR

- A concern with using this definition is that it takes months for LN to respond, and if a patient is resistant, that determination would be made too late.

- Alvarado AS, et al. *Lupus*. 2014.

- A post hoc analysis of the ALMS trial suggested that:

- If proteinuria does not decline by at least 25% after 8 weeks of treatment, a patient is unlikely to respond (odds ratio of 2.9) to that regimen.

- Dall'Era M, et al. *Arthritis Rheumatol*. 2015

- If the patient is experiencing a rapid deterioration of renal function, it would be prudent to change therapy sooner.

- The timing of when to change induction therapy is not clear, and clinical judgment should prevail.

Factors to consider in refractory lupus nephritis

- **Adherence with medication**

- Less organ damage in the long term as a result of the better doctor-patient interaction with active patient participation.
- Ward MM, et al. Arthritis Rheum 2003

- Non-compliance was a significant factor in determining renal morbidity
- Petri M, et al. Am J Med 1991

Factors to consider in refractory lupus nephritis

- **Tolerability of therapy and adverse events**

- Serious adverse events are frequent in LN and may be treatment related or unrelated, but whatever the cause they may result in interruption of effective therapy and loss of disease control.

Factors to consider in refractory lupus nephritis

- **Late presentation when irreversible disease**
- Early diagnosis of renal involvement in SLE results in better treatment response.
- Delayed diagnosis is more likely to lead to refractory LN.
- Chronic damage to the kidney accumulates early in LN.

Factors to consider in refractory lupus nephritis

- Optimization of immunosuppressive dosing for a poor therapeutic response.

Factors to consider in refractory lupus nephritis

- **Pathology:**
- Proliferative lupus nephritis and renal impairment or adverse histologic features such as crescents and fibrinoid necrosis in 25% or more of glomeruli,

- ALMS maintenance trial, showed a trend for more adverse kidney outcomes after 3.5 years in patients induced with MMF compared with those induced with cyclophosphamide.

- Other studies have also shown higher relapse rates and more patients going on to ESRD after induction with MMF.

- Dooley MA, et al. *N Engl J Med*. 2011
- So MW, et al. *Clin Rheumatol*. 2011

- Epidemiologic studies evaluating progression of LN to ESRD have not found a substantial benefit in the era of widespread MMF use; rather, there appears to have been an uptick in the incidence of ESRD during these years.

- Tektonidou MG, et al. Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971–2015: A Systematic Review and Bayesian Meta-Analysis. *Arthritis Rheumatol*. 2016

Factors to consider in refractory lupus nephritis

- **Decoupling of autoimmunity and end-organ damage**
- supported by data from the characterization of multiple congenic strains of New Zealand Mixed (NZM) mice.
- Genetic Data Support the Thesis That Acute Glomerulonephritis Need Not Progress to Chronic Glomerulonephritis
- Ge Y, et al. *J Exp Med*. 2013

TREATMENT

- Once a disease is considered refractory/resistant several treatment options have been proposed, but none of these has been tested in a controlled trial.

Refractory Lupus Nephritis

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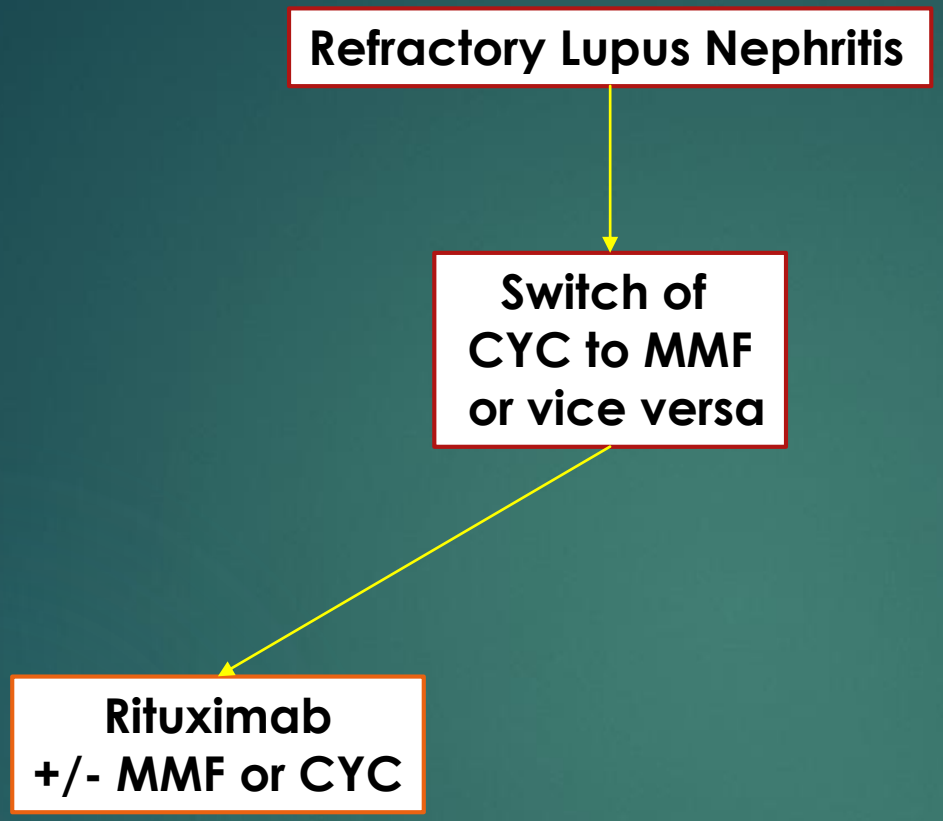
Switch of CYC to MMF or vice versa


Refractory Lupus Nephritis
Switch of CYC to MMF or vice versa
Rituximab +/- MMF or CYC

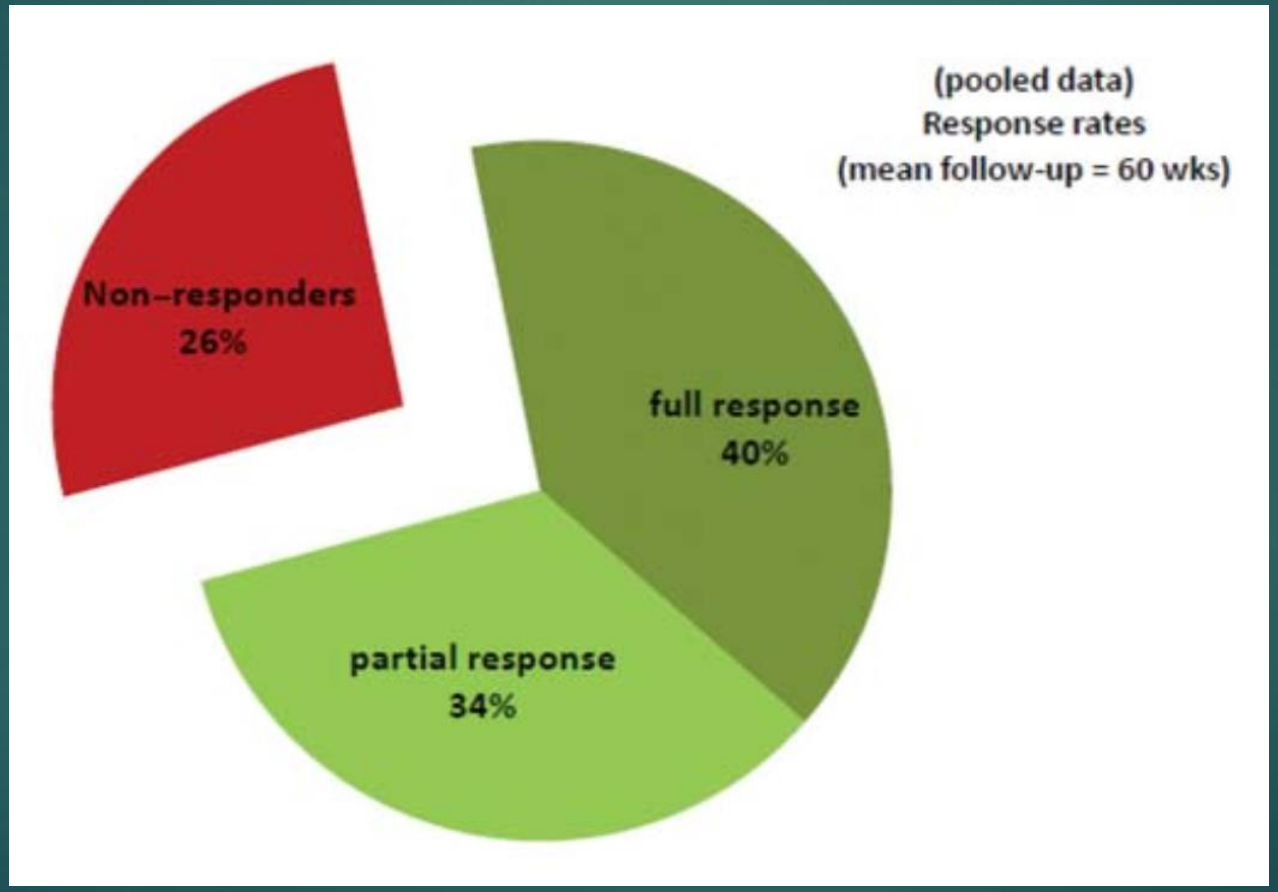
Rituximab

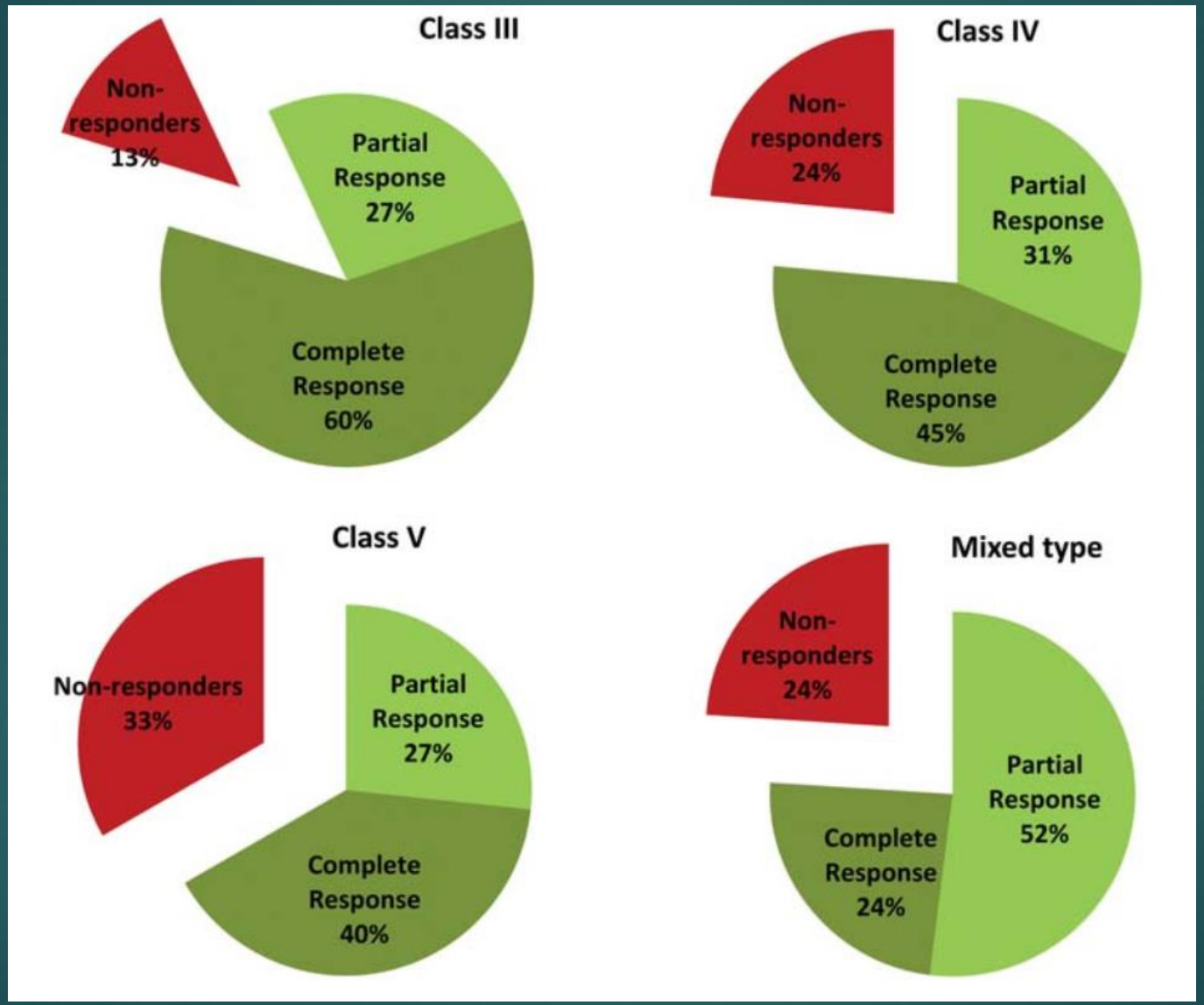
- Rituximab and novel strategies Despite the failure of a randomized controlled trial, rituximab has shown encouraging results in the treatment of refractory LN.

Rituximab

- A total of 300 patients were reported in the 26 studies.
- Among the 26 studies retrieved, 9 were prospective clinical trials.
- RTX was not uniformly given as an alternative or add-on therapy.
  - 30% received cyclophosphamide along with RTX,
  - 25% received mycophenolate mofetil
  - 7% received azathioprine
  - 4% received methotrexate

- Weidenbusch M, et al. Nephrol Dial Transplant 2013


(pooled data)
Response rates
(mean follow-up = 60 wks)
Non–responders
26%
full response
40%
partial response
34%

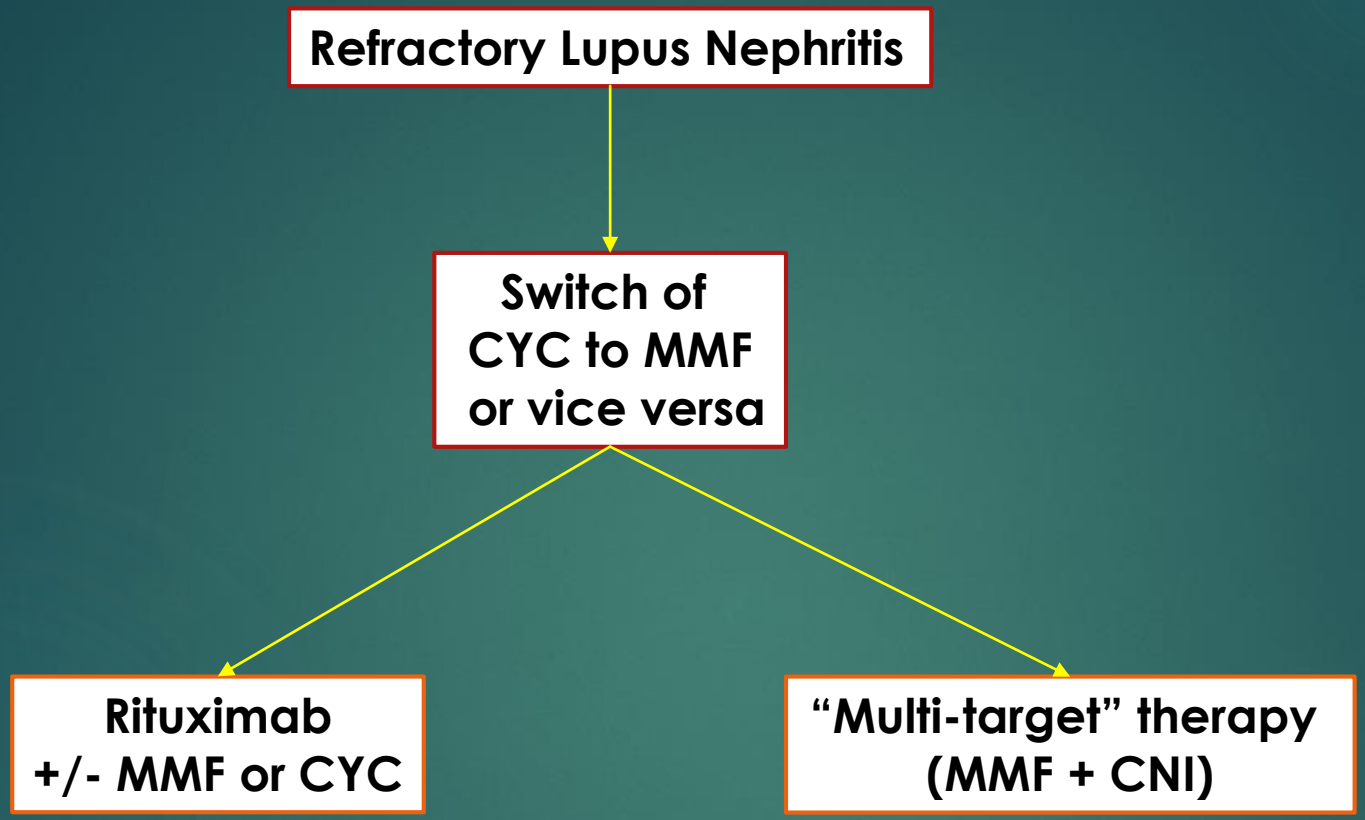

Class III
Non-responders 13%
Partial Response 27%
Complete Response 60%
Class IV
Non-responders 24%
Partial Response 31%
Complete Response 45%
Class V
Non-responders 33%
Partial Response 27%
Complete Response 40%
Mixed type
Non-responders 24%
Partial Response 52%
Complete Response 24%

Country	Definition refractory LN	Number (patients)	Response rate (CRR/ PRR)	Side effects
Mexico [7]	#1	13	76.8% (38.4%/ 38.4%)	LON (7.7%)
Mexico [8]	#1	22	54.5% (22.7%/ 31.8%)	Histoplasmosis (4.5%)
Colombia [9]	#1	32	64% (28%/36%)	39.3%*
Singapore [10]	#2	7	100% (42.9%/57.1%)	–
Korea [11]	#3	17	64.7% (0%/64.7%)	Infusion reaction (10.3%), infections (7.7%)*[1]
China [37]	Undefined	42	83.3% (64.3%/19%)	not reported
Sweden [12]	#4	7	57.1% (42.9%, 14.2%)	Neutropenic fever, infections (28.6%)
United Kingdom [14]	#5	6	100%	Serum sickness syndrome (9.1%), HACA production (9.1%)*[1]
United Kingdom [13]	#5	11*[2]	91% (36.4%, 54.5%)	Infusion reaction (45.2%), infections (25.8%), LON (3.2%)
France [15]	#6	32 (42)*	74% (45%, 29%)*[3]	Infusion reaction (16.2%), thromboembolic event (4.4%), severe infection (8.8%)*[4]
France [16]	#7	12	50% (25%/25%)	Infections (8.3%), LON (16.7%), PRES and cerebral haemorrhage (8.3%)
Spain [17]	#8	63	82.5%	38.9% (mainly infections and infusion reactions)*[1]
Italy [39]	#1	68	94.1% (30.9%/ 63.2%)	Severe adverse events (15/134)*[5]
France [40]	#6	17	53%	*Escherichia coli* pyelonephritis (5.9%)
Japan [18]	#9	36	83.3%	Brain haemorrhage (1.7%), cerebral infarction (1.7%), sepsis (1.7%), Infections (25%), neutropenia (1.7%), myocardial infarction (1.7%)*[6]

Andreas Kronbichler, et al. Refractory lupus nephritis: When, why and how to treat. Autoimmunity Reviews 2019

- Ofatumumab
  - novel completely humanised CD20- depleting agent

- Thornton CC, et al. Ofatumumab: a novel treatment for severesystemic lupus erythematosus. Rheumatology (Oxford) 2015


Refractory Lupus Nephritis
Switch of CYC to MMF or vice versa
Rituximab +/- MMF or CYC
“Multi-target” therapy (MMF + CNI)

“Multi-target” therapy

- Addition of tacrolimus or cyclosporine A to other immunosuppressive measures has been proven to be efficacious especially in patients with difficult to treat diffuse proliferative or membranous LN

- Most of the evidence so far has been published in an Asian population and there is a strong need to prove this concept in other ethnicities.

Country	Definition refractory LN	Number (patients)	Response rate (CRR/ PRR)	Side effects
China [57]	Not defined	20	90% (50%/40%)	Infections (20%), new onset hypertension (15%), leukopenia (10%), gastrointestinal symptoms (10%), new onset diabetes mellitus (5%)
Spain [58]	#6	17	70% (35%/35%)	Leucopenia (2.9%), gastrointestinal side effects (23%), tremor (1.4%)*
China [59]	#6	26	88.5% (38.5%/50%)	Aspergillosis/CMV (3.8%), new onset hypertension (3.8%), alopecia (3.8%)
Korea [60]	#4	9	78% (22%/56%)	Tremor (77.7%), new onset diabetes mellitus (11.1%)
USA [61]	#6	7	57.1% (14.3%/42.8%)	Infections (57.1%), diabetic ketoacidosis (14.3%)
Japan [62]	#5	26	61.5%*[1]	New onset hypertension (15.3%), renal dysfunction (11.9%)*[1]
Portugal [63]	#6	6	83.4% (66.7%/16.7%)	No adverse events

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Extracorporeal treatment

- A reasonable option in patients with a refractory disease course or in whom a more aggressive treatment regimen is contraindicated (i.e., with concomitant severe infectious complications).

Stem cell transplantation

- As reported in the EBMT/EULAR registry was mainly used when damage accrual was already present.

- This may explain the high procedure-related mortality and due to a severe disease course the high rate of relapse following autologous stem cell transplantation.

Alternative therapy

- Leflunomide
- High-dose CYC (50 mg/kg for 4 days)
- Mizoribine (inosine monophosphate dehydrogenase inhibitor)
- IVIG (1–6 courses)
- Bortezomib (a proteasome inhibitor)

- Andreas Kronbichler, et al. Refractory lupus nephritis: When, why and how to treat. Autoimmunity Reviews 2019

Personalized (precision) medicine

- Genomic, Transcriptomic, Proteomic and Metabolomics data

- *Mariele Gatto, et al.* New therapeutic strategies in systemic lupus erythematosus management. *Nature Reviews Rheumatology 2019.*

Conclusion

- The treat-to-target initiative in SLE recommended that prevention of damage accrual is a major therapeutic goal, since damage leads to morbidity and is associated with mortality, especially in patients with SLE and end stage renal disease.


ای که الفبای زندگی را از سرچشمه نگاهت آموختم
روزت مبارک