Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-406 Voclosporin

Stand: Januar 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Kriterien gemäß 5. Kapitel § 6 VerfO	**Voclosporin [Lupus Nephritis]**
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss zur Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI – Off-Label-Use Mycophenolatmofetil/Mycophenolensäure bei Lupusnephritis (Beschluss vom 11.04.2017)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Voclosporin Lupkynis®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Lupkynis® ist in Kombination mit immunsuppressiven Basistherapien zur Behandlung von erwachsenen Patienten mit Lupusnephritis der Klasse III, IV oder V (einschließlich der gemischten Klassen III/V und IV/V) indiziert.
Biologika	
Belimumab Benlysta®	Benlysta ist indiziert als Zusatztherapie bei erwachsenen Patienten mit aktivem, Autoantikörper-positivem systemischem Lupus erythematodes (SLE), die trotz Standardtherapie eine hohe Krankheitsaktivität (z. B. positiver Test auf Anti-dsDNA-Antikörper und niedriges Komplement) aufweisen. Benlysta ist in Kombination mit immunsuppressiven Basistherapien zur Behandlung von erwachsenen Patienten mit aktiver Lupusnephritis indiziert.
Antimalariamittel	
Chloroquin Resochin®	Systemischer Lupus erythematodes.
Hydroxychloroquin Quensyl®	Systemischer Lupus erythematodes
NSAID – u.a. Indometacin; Ibuprofen	
Indometacin Indomet-ratiopharm®	Symptomatische Behandlung von Schmerz und Entzündung bei • akuten Arthritiden (einschließlich Gichtanfall)
Ibuprofen	Symptomatische Behandlung von Schmerz und Entzündung bei

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ibuprofen STADA®	• akuten Arthritiden (einschließlich Gichtanfall) Sonstige Hinweise Ibuprofen STADA® sollte nur unter strenger Abwägung des Nutzen-Risiko-Verhältnisses angewendet werden: • bei systemischem Lupus erythematodes (SLE) […]
Glucocorticoide – u.a. Prednisolon, Prednison, Betametason	
Prednisolon Prednisolon-ratiopharm®	Erkrankungen der Haut und Schleimhäute, die aufgrund ihres Schweregrades und/oder Ausdehnung bzw. Systembeteiligung nicht oder nicht ausreichend mit topischen Glucocorticoiden behandelt werden können. Dazu gehören: - Autoimmunerkrankungen: z. B. […] chronisch discoider und subakut cutaner Lupus erythematodes (DS: b –a) aktive Phasen von rheumatischen Systemerkrankungen (DS: a, b): systemischer Lupus erythematodes, […]
Betamethason CELESTAMINE®	Orale Anfangsbehandlung von Autoimmunerkrankungen wie systemischer Lupus erythematodes (insbesondere viszerale Formen). Dosierung: Aktive Phasen von rheumatischen Systemerkrankungen: Systemischer Lupus erythematodes 6–15mg/Tag.
Immunsuppressiva	
Azathioprin Azathioprin-ratiopharm®	Azathioprin ist in Fällen der folgenden Erkrankungen bei Patienten, die Steroide nicht vertragen, die steroidabhängig sind oder bei denen trotz hochdosierter Behandlung mit Steroiden keine ausreichende oder nachhaltige therapeutische Wirkung erzielt werden kann, angezeigt: - systemischer Lupus erythematodes.
Zytostatika	
Cyclophosphamid Endoxan®	Bedrohlich verlaufende „Autoimmunkrankheiten“: Schwere, progrediente Formen von Lupus Nephritis und Wegener-Granulomatose. Eine Behandlung von Lupus Nephritis und Wegener-Granulomatose mit Endoxan® sollte nur durch Ärzte erfolgen, die über spezielle Erfahrungen zu den Krankheitsbildern und zu Endoxan® verfügen.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-406 (Voclosporin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. Januar 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azathioprin
CYC	Cyclophosphamid
ESKD	end-stage kidney disease
G-BA	Gemeinsamer Bundesausschuss
GFR	glomeruläre Filtrationsrate
GIN	Guidelines International Network
GoR	Grade of Recommendations
HCQ	Hydroxychloroquin
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LN	Lupus nephritis
MMF	Mycophenolatmofetil
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds Ratio
RR	Relatives Risiko
RTX	Rituximab
SIGN	Scottish Intercollegiate Guidelines Network
SLE	systemischer Lupus erythematodes
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Systemischer Lupus erythematodes (inkl. Lupus-Nephritis).

Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Systemischer Lupus erythematodes (inkl. Lupus-Nephritis).* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinien-organisationen. Ergänzend wurde eine freie Internetsuche (https://www.ecosia.org/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 26.11.2021 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 857 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 13 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Tunnicliffe DJ et al., 2018 [12].

Immunosuppressive treatment for proliferative lupus nephritis.

Fragestellung

To assess the evidence and evaluate the benefits and harms of different immunosuppressive treatments in people with biopsy-proven lupus nephritis.

1. Are new immunosuppressive agents superior to or as effective as cyclophosphamide plus corticosteroids?
2. Which agents, dosages, routes of administration and duration of therapy should be used?
3. Which toxicities occur with the different treatment regimens?

Methodik

Population:

- adults and children with biopsy-proven proliferative lupus nephritis

Intervention/Komparator:

following treatment options for either induction or maintenance therapies for lupus nephritis:

- Corticosteroids including prednisone and methylprednisolone
- Other immunosuppressive agents including azathioprine, cyclophosphamide, MMF, tacrolimus and cyclosporin
- Plasma exchange or plasmapheresis
- Biologic therapy (for example, abatacept, atacicept, laquinimod, ocrelizumab, rituximab and sirukumab).

Endpunkte:

Primary outcomes:

- Death (all causes)
- end-stage kidney disease (ESKD), requirement for renal replacement therapy
- Complete renal remission: defined as return to normal SCr, urinary protein excretion < 0.5 g/24 h, and inactive urinary sediment) following induction therapy
- Relapse of lupus nephritis: maintenance therapy

Secondary outcomes:

- Partial renal remission: defined as a fall to < 3.0 g/d protein if baseline ≥ 3.0 g/d or ≥ 50% reduction if < 3.0 g/d at baseline and stabilisation of SCr ± 25%
- Remission in proteinuria: complete and partial.
  - Complete remission in proteinuria: defined as urinary protein excretion ≤ 0.3 g/24 h
  - Partial remission in proteinuria: defined as < 3.0 g/d protein if baseline ≥ 3.0 g/d or ≥ 50% reduction if < 3.0 g/d at baseline

Recherche/Suchzeitraum:

- Up to 03/2018

- RCTs and quasi-RCTs were included

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Evidence certainty was determined using GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- In this review update, 26 new studies were identified, to include 74 studies involving 5175 participants overall

Qualität der Studien:

- most studies had high or unclear risks of bias for most domains of study reporting assessed
- The internal validity of the design, conduct and analysis of the included RCTs was difficult to assess in some studies because of the omission of important methodological details.
- No study adequately reported all domains of the risk of bias assessment so that elements of internal bias may be present in the meta-analysis

Studienergebnisse:

Ergebnisdarstellung beschränkt auf zugelassene Interventionen bzw. Interventionen mit Off-label-Use-Beschluss

Induction therapy

MMF + corticosteroids vs. cyclophosphamide + corticosteroid (10 studies, 878 participants)

- No stat sign difference in death: RR 1,12 [95%CI 0,61; 20,6); very low certainty of evidence
- No stat sign difference in ESKD: RR 0,71 (0,27; 1,84); very low certainty of evidence
- Compared with intravenous (IV) cyclophosphamide, MMF may have increased complete disease remission (RR 1.17, 95% CI 0.97 to 1.42; low certainty evidence), although the range of effects includes the possibility of little or no difference.
- Compared to IV cyclophosphamide, MMF is probably associated with
  - decreased alopecia (RR 0.29, 95% CI 0.19 to 0.46) (moderate certainty evidence),
  - increased diarrhoea (RR 2.42, 95% CI 1.64 to 3.58) (moderate certainty evidence) and
  - no difference to major infection (RR 1.02, 95% CI 0.67 to 1.54; (low certainty evidence).
- It is uncertain if MMF decreased ovarian failure compared to IV cyclophosphamide because the certainty of the evidence was very low (RR 0.36, 95% CI 0.06 to 2.18).

MMF + IV cyclophosphamide + corticosteroids versus IV cyclophosphamide + corticosteroids (1 study; n=82)

- No stat sign difference in death: RR 0.95 [0.06, 14.72]; very low certainty of evidence
- No stat sign difference in remission; very low certainty of evidence
- major infection RR 0.37, 95% CI 0.14 to 0.93)

Cyclophosphamide + corticosteroid versus azathioprine + corticosteroids (4 studies, n=219)

- The risk of death at five years (RR 1.39 [0.25, 7.77], 2 studies, 146 participants) and at 10 years (RR 1.93 [1.22, 3.06], 1 study, 59 participants) is uncertain because the certainty of the evidence was very low.
- it is uncertain if azathioprine compared to cyclophosphamide reduced ESKD (RR 0.40 [0.15, 1.07], 2 studies, 144 participants).

IV cyclophosphamide + corticosteroid versus corticosteroid alone (5 studies, 261 participants

- death: RR 0.98 [0.53, 1.82], 5 studies
- ESKD: RR 0.63 [0.39, 1.03]; 5 studies
- Complete remission of proteinuria. RR 2.63 [0.13, 54.64]; 1 study
- Major infection: RR 0.87 [0.50, 1.51]; 6 studies

Cyclophosphamide + azathioprine + corticosteroids versus corticosteroid alone (1 study, n=29)

- death: RR 0.53 [0.17, 1.68],
- ESKD: RR 0.21 [0.04, 1.02]
- Major infection: RR 0.48 [0.10, 2.30]

Azathioprine + corticosteroids versus corticosteroids alone (3 studies, 78 participants

- death: RR 0.60 [0.36, 0.99]
- ESKD: RR 0.66 [0.17, 2.55]
- Complete remission of proteinuria. RR 0.95 [0.54, 1.69]

Maintenance therapy

- 9 studies (767 participants; median 30 months duration (range 6 to 63 months))

Azathioprine + corticosteroid versus MMF + corticosteroid

- No stat sign difference in death: RR 1,15 (0,34; 3,87) very low certainty of evidence
- No stat sign difference in ESKD; RR 1,70 (0,52; 5,54); very low certainty of evidence
- Superiority of MMF in renal relapse: RR 1.75, 95% CI 1.20 to 2.55; moderate certainty evidence).
- No stat sign difference in Major infection: RR 1,08 (0,69; 1,96); low certainty of evidence
- No stat sign difference in Alopecia: RR 0,95 (0,46; 1,95), low certainty of evidence

Multiple other interventions were compared as maintenance therapy, but patient-outcome data were sparse leading to imprecise estimates.

Anmerkung/Fazit der Autoren

In this review update, studies assessing treatment for proliferative lupus nephritis were not designed to assess death (all causes) or ESKD. The effects of all treatment strategies on death (all causes) and ESKD were uncertain (very low certainty evidence) as this outcome occurred very infrequently.

MMF may lead to increased complete disease remission compared with IV cyclophosphamide, with an acceptable adverse event profile, although evidence certainty was low and included the possibility of no difference. Calcineurin combined with lower dose MMF may improve induction of disease remission compared with IV

cyclophosphamide, but the comparative safety profile of these therapies is uncertain. Azathioprine may increase disease relapse as maintenance therapy compared with MMF

Kommentare zum Review

- Patientenpopulation: Sowohl Kinder und Erwachsene eingeschlossen: 29 studies included children under the age of 18 years with lupus nephritis, however only two studies exclusively examined the treatment of lupus nephritis in patients less than 18 years of age

3.2 Systematische Reviews

Teng et al. 2021 [11]

Efficacy and safety of an anti-CD20 monoclonal antibody, rituximab, for lupus nephritis: A meta-analysis.

Fragestellung

To compare the efficacy and safety of RTX with those of conventional medicines as an induction therapy for LN.

Methodik

Population:

- Participants aged 18 years old or older with LN

Intervention vs. Komparator:

- RTX vs. placebo or other immune suppressors

Endpunkte:

- Complete renal remission
- partial renal remission
- total renal remission (the sum of complete renal remission and partial renal remission or following definition given in the ordinary studies by the end of 6 or 12 months)
- drug-related AE such as infection, leukopenia, gastrointestinal symptoms

Recherche/Suchzeitraum:

- Medline, Embase, and the Cochrane Library database to June 2021

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 studies (N=588 patients)
  - 3 studies compared the efficacy of RTX vs. MMF vs. CYC
  - 1 study compared RTX vs. placebo
  - 2 studies compared RTX vs. CYC

Charakteristika der Population:

TABLE 1 Characteristics of the studies included in the meta-analysis

Study	ISN/RPS class	Country	Follow-up (m)	Total cumulative dose of RTX	Mean age (y)	RTX/CYC/MMF	
						Baseline Scr (mg/dL)	Baseline proteinuria (g/24 h)
Dario 2021[21]	IV/III+V/V	Italy	12	NA	NA	0.9/1.0/0.8[a]	5/5.2/4.6[a]
Gabriella 2012[15]	III/IV/III+V/IV+V	Italy	12	2 g	NA	0.8/0.8[a]	4.8/3.4[a]
Gabriella 2014[7]	III/IV/V/III+V/IV+V	Italy	12	2 g	35.0 ± 10.2	1.1 ± 0.8/0.9 ± 0.3/1.2 ± 1.0	4.5 ± 2.9/3.3 ± 2.2/3.5 ± 2.9
LUNAR 2012[19]	III/IV/III+V/IV+V	Latin America	12	4 g	30.6 ± 9.5	1.0 ± 0.5/1.0 ± 0.5	NA
Rudra 2018[20]	III/IV/V/III+V/IV+V	India	6	1.9 g	25.9 ± 8.9	1.2 ± 0.6/1.1 ± 0.7/1 ± 0.5	3.5 ± 2.7/2 ± 1.7/2 ± 1.8
Zhang 2015[16]	III+V/IV+V	China	12	2.6 g	38.9 ± 6.6	1.3 ± 0.4/1.3 ± 0.4	4.8 ± 1.9/4.9 ± 1.8

Abbreviations: CYC, cyclophosphamide; MMF, mycophenolate mofetil; NA, not acquired; RTX, rituximab; Scr, serum creatinine.
[a]The numbers reported refer to median.

Induction treatment		Sample size	Refractory LN or previous relapses (%)		Patients receiving RTX as additional therapy (%)
			RTX	Control	
RTX (375 mg/m^2 on d 2, 8, 15, 22, 52 and 82) + CYC (10 mg/kg at d 4 and 17)	CYC (0.5 g each for a total of 6 administrations)/MMF (2-3 g/d)	30/10/20	50%	50%	100%
RTX (1 g at d 3, 18)	CYC (1-2 mg/kg/d for 3 mo)	10/14	100%	100%	0
RTX (1 g at d 3, 18)	CYC (0.5 g each for a total of 6 administrations)/MMF (2-2.5 g/d)	17/20/17	59%	70%	0
RTX (1 g at d 1, 15, 168, 182) + MMF (initiated with 0.5 g 3/d, increased to 3 g/d by 4 wks and until to at least wk 52)	MMF (initiated with 0.5 g 3/d, increased to 3 g/d by 4 wks and until to at least wk 52)	72/72	NA	NA	100%
NA	CYC (low dose: 6 biweekly pulses of 500 mg; high dose: 6 pulses of 750-1200 mg monthly)/MMF (1.5-3 g/d)	22/139/61	NA	NA	73%
RTX (375 mg/m^2 at wks 0, 2, 4, 6) + CYC (0.8 g at wks 1, 3)	CYC (0.8 g/mo)	42/42	100%	100%	100%

Qualität der Studien:

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other source
Dario 2021[21]	high	high	high	low	low	low
Rudra 2018[20]	high	high	high	low	low	high
Gabriella 2014[7]	high	high	high	low	low	low
LUNAR 2012[19]	unclear	unclear	unclear	low	low	unclear
Zhang 2015[16]	unclear	unclear	unclear	low	low	unclear
Gabriella 2012[15]	high	high	high	low	low	low

Assessment of risk bias according to the Cochrane Collaboration's tool, low risk of bias was represented as "LOW" and high risk of bias was "HIGH"

Studienergebnisse:

Total and complete renal remission

- RTX increased total (OR 2.16, 95% CI 1.31 to 3.55, p=.003) and complete renal remission (OR 2.42, 95% CI 1.18 to4.94, p=.02) compared with control group
- RTX was more effective at increasing the rates of total renal remission and complete renal remission for LN patients compared with MMF (total renal remission: OR 4.6, 95% CI 1.29 to 16.47, p=.02; complete renal remission: OR 2.56, 95% CI 1.19 to 5.47, p=.02) and CYC (total renal remission: OR 2.89, 95% CI 1.31 to 6.40, p=.009; complete renal remission: OR 2.75, 95% CI 1.19 to 6.4, p=.02)

Anmerkung/Fazit der Autoren

This study provides clear beneficial effects of RTX induction therapy in patients with LN. In addition, RTX therapy did not increase the risk of adverse events compared to the control group.

Jiang Y-P et al., 2020 [7].

Comparative efficacy and safety of mycophenolate mofetil and cyclophosphamide in the induction treatment of lupus nephritis - A systematic review and meta-analysis

Fragestellung

To evaluate the efficacy and safety of MMF vs CYC as induction therapy for LN, we performed a meta-analysis by pooling the results of all the current randomized controlled trials (RCTs).

Methodik

Population:

- LN set by the American College of Rheumatology (ACR), and the renal biopsy of LN in patients can be classified into stage III-V

Intervention vs. Komparator:

- Induction treatments for the case and control groups were respectively MMF vs. CYC or MMF/CYC combined with other drugs which were the same in both groups

Endpunkte:

- Urine protein (UPRO), serum creatinine and serum complement C3. Complete remission, ADRs including infection, leukopenia, menstrual disorders and digestive tract symptoms such as diarrhea, nausea and vomiting

Recherche/Suchzeitraum:

- PubMed, EMBASE, Wiley, Cochrane library to Nov. 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 19 RCTs (N=1989)

Charakteristika der Population:

- 10 studied MMF/CYC, 8 related to MMF/CYC combined with glucocorticoids, 1 studied concerning MMF/CYC combined with hydroxychloroquine.
- LN subjects included in the RCTs were aged 15 to 48, whose pathological stage all belonged to type III–V according to the standards of WHO/ISN. Besides, among all the patients, 825 were Asian and 1164 were Caucasian.

Qualität der Studien:

Table 2

Risk of bias of included studies according to the Cochrane Risk of Bias tool.

Author/year	Randomization	Allocation concealment	Blinding of assessor and/or physician (for assessment of objective outcomes)	Blinding of participants (for assessment of subjective outcomes)	Intention to treat	Selective outcome report	Free of other bias
Li et al.(2012)	Yes	Unclear	No	No	Yes	Yes	Yes
El-Shafey et al (2010)	Yes	Unclear	No	No	Yes	Yes	Unclear
Rathi M et al (2015)	Yes	Unclear	No	No	Yes	Yes	Unclear
Chan TM et al (2001)	Yes	Unclear	No	No	Yes	Yes	Unclear
Wang J et al (2007)	Yes	Unclear	No	No	Yes	Yes	Unclear
Elliott JR et al (2006)	Yes	Unclear	No	No	Yes	Yes	Unclear
Chan TM et al (2005)	Yes	Unclear	No	No	Yes	Yes	Unclear
Arun S et al (2018)	Yes	Unclear	No	No	Yes	Yes	Unclear
Feng X et al (2014)	Yes	Unclear	No	No	Yes	Yes	Unclear
Liu Z et al (2014)	Yes	Unclear	No	No	Yes	Yes	Unclear
Radhakrishnan J et al (2010)	Yes	Unclear	No	No	Yes	Yes	Unclear
Mendonca S et al (2017)	Yes	Unclear	No	No	Yes	Yes	Unclear
Walsh M et al (2013)	Yes	Unclear	No	No	Yes	Yes	Unclear
Ginzler EM et al (2006)	Yes	Unclear	No	No	Yes	Yes	Unclear
Appel GB et al (2009)	Yes	Unclear	No	No	Yes	Yes	Unclear
Ginzler EM et al (2010)	Yes	Unclear	No	No	Yes	Yes	Unclear
Ong LM et al (2005)	Yes	Unclear	No	No	Yes	Yes	Unclear
Bao H et al (2008)	Yes	Unclear	No	No	Yes	Yes	Unclear

Studienergebnisse:

Complete remission

- A total of 11 studies examines complete response after treatment in both groups. Meta-analysis showed that MMF could better increase the complete remission [(RR=1.415, 95%CI (1.231–1.626)].

Infection

- The incidence of infection in MMF group was lower than that of CYC in Caucasian patients [RR=0. 727, 95%CI (0.532–0.993)] rather than in Asian patients ([RR=0.972, 95%CI (0.753–1.255)],

Leukopenia

- The results showed that the incidence of leukopenia in MMF group was significantly decreased in Asian patients [RR= 0.187, 95%CI (0.077–0.452)], rather than in Caucasian patients [RR=0.634, 95%CI (0.396–1.014)] when compared with CYC group (P=.057).

Menstrual abnormalities

- 9 studies described the occurrence of abnormal menstruation. There were 6 articles from Asian patients, and 3 from Caucasian patients.
- The results illustrated that the frequency of abnormal menstruation in MMF group was lower than CYC group in Asian patients [RR=0.238, 95%CI (0.107–0.531)] rather than in Caucasian patients [RR= 0.601, 95%CI (0.292–1.235)] (P=.166),

Gastrointestinal symptoms.

- A total of 10 articles described the incidence of gastrointestinal symptoms. The result revealed that the incidence of digestive tract symptoms in CYC group was significantly higher than that of MMF group [RR= 0.639, 95%CI (0.564–0.724)] but accompanied with a high heterogeneity (I2=79.6% >50%).
- Subgroup analysis showed that the incidence of gastrointestinal symptoms caused by MMF was lower than that of CYC both in Asian patients [RR=0.257, 95%CI (0.166–0.399)] and Caucasian patients [RR=0.765, 95%CI (0.674–0.869)], but the former was associated with a lower heterogeneity (I2=4.6%)

Anmerkung/Fazit der Autoren

MMF is a better choice for adolescent or reproductive patients of LN with low serum complement C3, susceptibility to infection and poor gastrointestinal function. While CYC tends to be superior for Asian patients and those with a low initial level of UPRO (<4g/day) when used to reduce UPRO. Besides, from the meta-analysis on side effects, we also infer that race should be taken into consideration with highest priority when choosing medication in clinic, so as to purposefully reduce side effects.

Kommentar zum Review

Vergleichbare Ergebnisse in der Publikation von Zhang H et al., 2020 [13].

Deng J et al., 2019 [2].

Maintenance therapy for lupus nephritis with mycophenolate mofetil or azathioprine. A meta-analysis

Fragestellung

to evaluate the efficacy and safety of mycophenolate mofetil (MMF) and azathioprine (AZA) as maintenance therapy for LN.

Methodik

Population:

a) patients diagnosed with LN by renal biopsy

Intervention/Komparator:

b) MMF and AZA as maintenance therapies

Endpunkte:

c) efficacy (mortality, end-stage renal disease (ESRD), relapse, and doubling of serum creatinine) and safety

Recherche/Suchzeitraum:

- from inception to October 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 studies (n=602) were included in the present meta-analysis

Qualität der Studien:

Table 2. Quality assessment of included studies.

Study	Chan 2000 [15]	Jiang 2002 [16]	Contreras 2004 [17]	Chan 2005 [18]	Houssiau 2010 [19]	Dooley 2011 [20]	Kaballo 2016 [21]
Random sequence generation	Unclear	Unclear	Low	Low	Low	Low	Low
Allocation concealment	Unclear	Unclear	Low	High	Unclear	Low	Low
Blinding of participants and personnel	Unclear	Unclear	High	High	Unclear	Low	Unclear
Blinding of outcome assessors	Unclear	Unclear	High	High	Unclear	Low	Unclear
Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low
Selective reporting	Low	Low	Low	Low	Low	Low	Low
Other sources of bias	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear

Low = low risk of bias; unclear = unclear risk of bias; high = high risk of bias.

Studienergebnisse:

Studiencharakteristika:

Table 1. Baseline characteristics of included studies.

Study	Chan 2000 [15]	Jiang 2002 [16]	Contreras 2004 [17]	Chan 2005 [18]	Houssiau 2010 [19]	Dooley 2011 [20]	Kaballo 2016 [21]
Enrolled, N (MMF/AZA)	21/21	25/21	20/19	32/30	53/52	116/111	41/40
Female, n (MMF/AZA)	20/19	24/19	19/18	26/26	48/48	99/96	38/37
Age, years (MMF/AZA)	36 ± 11/ 39 ± 9	37 ± 10/ 39 ± 11	32 ± 11/ 33 ± 10	38.1 ± 10.2/ 41.8 ± 8.9	33 ± 10/ 33 ± 11	31.8 ± 10.59/ 31.0 ± 10.77	27.1 ± 9.8/ 29.4 ± 11.6
Proteinuria, g/d (MMF/AZA)	5.8 ± 4.6/ 3.7 ± 1.7	5.7 ± 4.7/ 3.9 ± 1.6	N/A	6.21 ± 4.11/ 4.44 ± 3.62	3.63 ± 2.80/ 2.94 ± 2.42	0.96 ± 0.82/ 0.82 ± 0.75	3.2 ± 2.1/ 3.2 ± 4
Serum creatinine, mg/dL (MMF/AZA)	1.2 ± 0.6/ 1.2 ± 0.3	1.2 ± 0.6/ 1.14 ± 0.3	1.16 ± 0.7/ 0.96 ± 0.5	1.27 ± 0.74/ 1.28 ± 0.53	1.01 ± 0.33/ 1.02 ± 0.47	0.82 ± 0.24/ 0.90 ± 0.38	1.5 ± 1.1/ 1.9 ± 1.5
Serum albumin, g/dL (MMF/AZA)	2.8 ± 0.6/ 2.8 ± 0.5	2.7 ± 0.6/ 2.8 ± 0.5	3.3 ± 0.5/ 3.5 ± 0.5	2.76 ± 0.67/ 2.75 ± 0.38	2.97 ± 0.66/ 3.01 ± 0.75	N/A	N/A
Pathology tape, class III (or III + IV)/IV (or IV + V)/V	MMF: 0/21/0 AZA: 0/21/0	MMF: 0/25/0 AZA: 0/21/0	4/16/0 6/13/0	0/62/0	16/31/6 17/30/5	17/81/18 12/82/17	32/49/0
Induction treatment	Prednisone 0.8 mg/ kg/d + either MMF 2 g/d or CYC 2.5 mg/kg/day × 6 months	Prednisone 1 mg/ kg/d + either MMF 2 g/d or IV CYC 20 mg/kg × 6 pulses	IV CYC 0.5 – 1 g/m^2 for 4 – 7 pulses	Prednisone 0.8 mg/ kg/d + either MMF 2 g/d or CYC 2.5 mg/ kg × 6 months	Pulse methylprednisolone + high.dose prednisone + IV CYC 500 mg × 6 doses	High-dose prednisone + IV CYC (6 pulses) or MMF (3 g/d) × 6 months	IV methylprednisolone (15 mg/kg/d) × 3 pulses + IV CYC 500 mg/m^2 × 6 months
Maintenance treatment	MMF: 1 g/d AZA: 1.5 mg/kg/d	MMF: 1 g/d AZA: 1.5 mg/kg/d	MMF: 0.5 – 3 g/d AZA: 1 – 3 mg/kg/d	MMF: 1 g/d AZA: 1.5 – 2 mg/kg/d	MMF: 2 g/d AZA: 2 mg/kg/d	MMF: 2 g/d AZA: 2 mg/kg/d	MMF: 22 mg/kg/d AZA: 2 mg/kg/d
Definition of relapse	By histologic studies	N/A	Doubling of protein: creatinine ratio ≥ 50% increase in serum creatinine from basal > 1 month; amenorrhea ≥ 12 months; hospitalization, infection, and other adverse events	By clinical manifestations indicating activity, with or without serologic reactivation	Proteinuria ≥ 0.3 g/d and albumin ≤ 3.5 g/dL; ≥ 33% increase in serum creatinine from baseline; proteinuria ≥ 300% accompanied by microscopic hematuria and reduction in C3 ≥ 33%	Doubling of urinary protein: creatinine ratio; proteinuria ≥ 25% increase in serum creatinine, accompanied by proteinuria ≥ 2 g/d or hematuria or cellular casts	≥ 50% increase in serum creatinine levels; doubling of proteinuria; ≥ 2 g/d increase in proteinuria
Ethnicity, White/Black/ Asian/Other (MMF/AZA)	0/0/42/0	0/0/46/0	1/9/0/10 2/9/0/8	0/0/62/0	42/6/5/0 41/7/4/0	48/12/39/17 51/11/37/12	0/81/0/0
Duration, months	12	12	72	63	48	36	36
Study characteristics	Single-center, national	Single-center, national	Single-center	Single-center, national	Multicenter, national	Multicenter, international	Multicenter, national

MMF = mycophenolate mofetil; AZA = azathioprine; CYC = cyclophosphamide; IV = intravenous; N/A = not available.

Efficacy outcomes for MMF vs AZA:

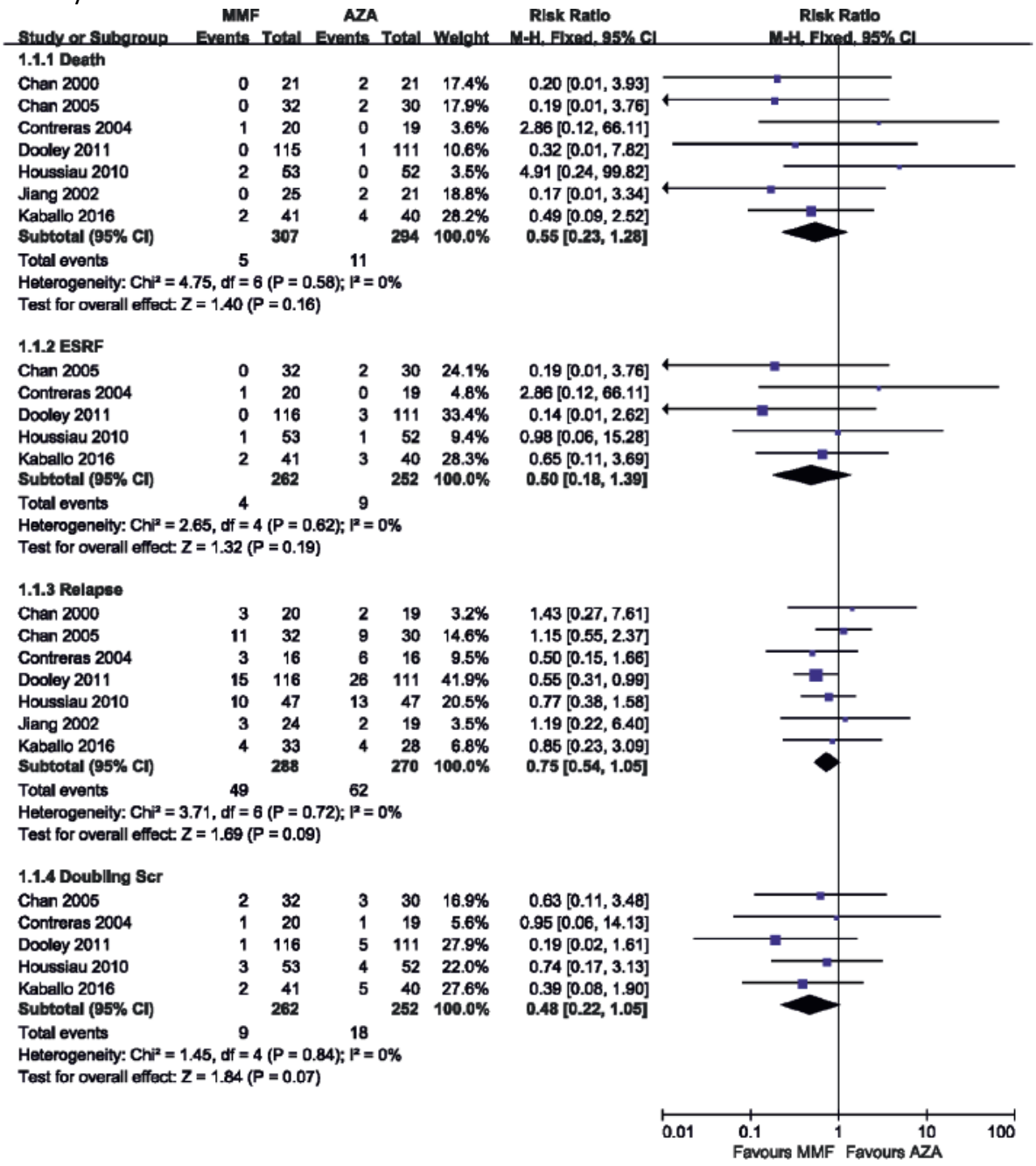

Figure 2. Prognosis of patients receiving mycophenolate mofetil (MMF) and azathioprine (AZA) in maintenance therapy.

Adverse events:

- no statistically significant difference in the outcomes of **infection** (RR = 0.61, 95% CI = 0.29 – 1.30; p = 0.20) or **gastrointestinal upset** (RR = 1.45, 95% CI = 0.84 – 2.53; p = 0.19).
- Fewer patients developed **leukopenia** (RR = 0.15, 95% CI = 0.06 – 0.36; p < 0.0001) and **amenorrhea** (RR = 0.23, 95% CI = 0.09 – 0.59; p = 0.002) in the **MMF group**.

Anmerkung/Fazit der Autoren

Results suggest that the MMF group incurred lower risks of mortality, relapse, ESRD, and doubling of serum creatinine than the AZA group, although differences did not reach

statistical significance. MMF significantly decreases the risks of leukopenia. The incidence of amenorrhea was lower with MMF than AZA. However, amenorrhea is not usually considered a common side effect of MMF or AZA. We found that patients in the azathioprine group received more cyclophosphamide treatment during induction therapy. This may explain the higher amenorrhea rate in the azathioprine group.

There were some heterogeneities among clinical features such as race, sex, age, the proportion of patients with class IV LN, and the definition of renal relapse. There were ethnic differences in disease and outcomes. LN shows greater mortality and higher prevalence among African American, Hispanic, Chinese, and other Asian populations [24]. We could not conduct a subgroup analysis based on ethnicity because of the limited available data in the primary literature.

Referenzen:
[24] *Lau CS, Yin G, Mok MY.* Ethnic and geographical differences in systemic lupus erythematosus: an overview. Lupus. 2006; *15:* 715-719.

Kommentare zum Review:

d) Zum Vergleich MMF vs. AZA siehe auch CR von Tunnicliffe et al. 2018 [12]

Liu B et al., 2019 [9].

Corticosteroids combined with doublet or single-agent immunosuppressive therapy for active proliferative lupus nephritis

Zielsetzung

[…] to assess whether the efficacy and safety of C + doublet IT is superior to that of C + single-agent IT in active proliferative LN.

Methodik

Population:

LN patients in whom there was a histologically (renal biopsy) confirmed diagnosis according to the World Health Organization (WHO) 1982 classification or the International Society of Nephrology/Renal Pathology Society 2003 classification regardless of whether they were adults or children.

Intervention/Komparator:

C + doublet versus single-agent IT

Primärer Endpunkt:

overall response rate (ORR, including the complete response rate (CRR) and the partial response rate (PRR))

Sekundäre Endpunkte:

- change from baseline in SLE Disease Activity Index (SLE-DAI) scores
- negative conversion ratio of anti-double-stranded DNA (anti-dsDNA)
- all-cause mortality
- total adverse events (Aes)
- serious Aes
- infections

- urinary tract infection
- varicella zoster virus infection
- leukopenia
- menstrual disorder
- infusion-related Aes

Recherche/Suchzeitraum:

The PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched to identify relevant RCTs published prior to March 2019 […].

Qualitätsbewertung der Studien:

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to estimate the overall quality of the evidence.

Ergebnisse

Anzahl eingeschlossener Studien: (⇨ Anhang Tabelle 1)

- Eleven randomized trials were eligible. […] involved 1855 participants.
- Two trials (402 participants) evaluated C combined with tacrolimus (4 mg daily) and MMF (1000 mg daily) [6,25].
- One trial (265 participants) evaluated C combined with voclosporin (23.7 mg or 39.5 mg twice a day) and MMF (2000 mg daily for some participants) [26].
- One trial (82 participants) evaluated C combined with cyclophosphamide (0.4 g/m² monthly) and MMF (1000 mg daily) [27].
- One trial (46 participants) evaluated C combined with laquinimod and MMF [28].
- Six trials evaluated C combined with biologics and MMF or cyclophosphamide, including 3 trials (247 participants) for rituximab (RTX) [7,29,30], 2 trials (432 participants) for abatacept [31,32], and 1 trial (381 participants) for ocrelizumab [33].

Charakteristika der Population:

Most of the participants had active proliferative LN except for patients in one trial that enrolled refractory LN patients.

Qualität der Studien: (⇨ Anhang Tabelle 2)

Studienergebnisse: (⇨ Anhang Tabelle 2)

Renal response

Ten trials [6,7,25-27,29-33] comprising 1651 participants and 10 trials [6,7,25,27-33] involving 1432 participants were included in the current meta-analysis performed to estimate the CRR and ORR, respectively. Compared with C + single-agent IT, C + doublet IT had a significantly higher CRR and ORR (RRs of 1.40 [95% CI, 1.09 to 1.79], $P < 0.01$, and 1.22 [95% CI, 1.09 to 1.35], $P < 0.01$, respectively).

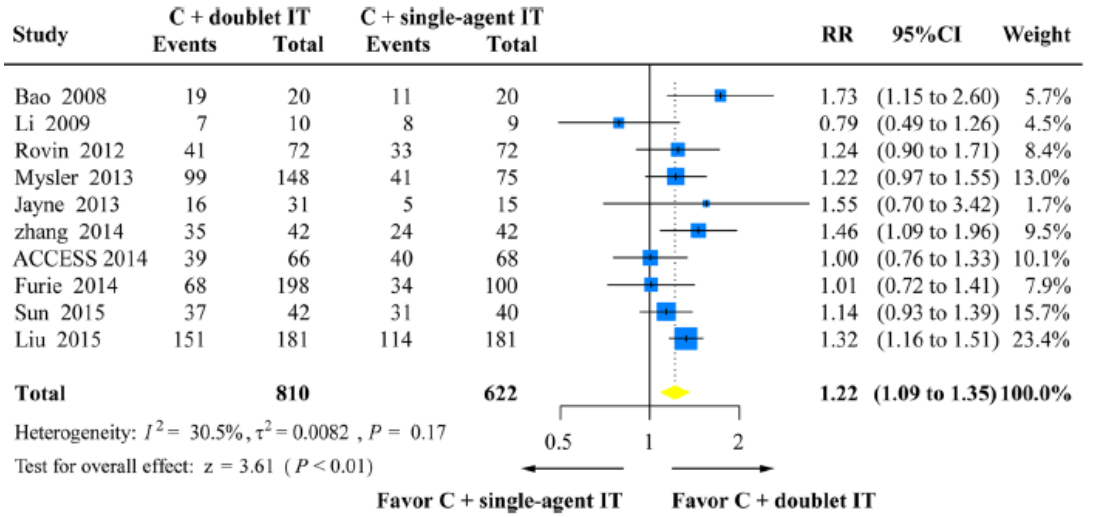

Abbildung 6: Overall response rate of the two treatments

In a subgroup analysis, C + doublet IT without biologics resulted in significantly higher CRR and ORR than were found for C + single-agent IT (RRs of 1.66 [95% CI, 1.21 to 2.29], P < 0.01, and 1.30 [95% CI, 1.13 to 1.50], P < 0.01, respectively), while C + doublet IT including biologics improved CRR and ORR only in refractory severe LN (RRs of 3.00 [95% CI, 1.61 to 5.58], P < 0.01, and 1.46 [95% CI, 1.09 to 1.96], P = 0.012, respectively). Among patients who received biologics in six trials [7,29-33] (902 participants), the type of accompanying immunosuppressive agent (i.e., cyclophosphamide or MMF) and the treatment duration did not influence the renal response (all P > 0.05).

The activity of SLE

The change from baseline in SLE-DAI scores and the negative conversion ratio of anti-dsDNA were reported in 2 trials [25,30] (446 participants) and 4 trials [6,25,32,33] (437 participants), respectively. The change from baseline in SLE-DAI scores was larger (standardized mean difference, -0.49; 95% CI, -0.68 to -0.30; P < 0.01), and the negative conversion ratio of anti-dsDNA was higher (RR, 1.34; 95% CI, 1.06 to 1.69; P = 0.014) for C + doublet IT than for C + single-agent IT.

Safety

We performed a pooled analysis of the 10 trials [6,7,25-29,31-33] (1768 participants) that evaluated the safety of the treatment regimens. There was no significant difference in all-cause mortality between C + doublet and single-agent IT (RR, 0.89; 95% CI, 0.43 to 1.85; P = 0.76). The risk for total AEs (RR, 1.01), serious AEs (RR, 1.08), infections (RR, 0.98), urinary tract infection (RR, 0.80), varicella zoster virus infection (RR, 1.37), upper respiratory tract infection (RR, 0.92), leucopenia (RR, 0.33), and infusion-related AEs (RR, 1.08) were similar between the two regimens (all P > 0.05). Compared with C + single-agent IT, C + doublet IT had a lower risk of menstrual disorder (RR, 0.38; 95% CI, 0.17 to 0.87; P = 0.022).

Tabelle 1: Safety between the two treatments

	No. of trials	No. of patients	RR (95% CI)	P value	I^2, %	GRADE
All AEs	6	1581	1.01 (0.96 to 1.06)	0.69	36	⊕⊕⊕◯ Moderate[b]
All-cause mortality	10	1768	0.89 (0.43 to 1.85)	0.76	14	⊕⊕⊕◯ Moderate[b]
Serious AEs	7	1627	1.08 (0.87 to 1.34)	0.49	22	⊕⊕⊕◯ Moderate[b]
Infections	6	1119	0.98 (0.83 to 1.16)	0.823	45.7	⊕⊕⊕◯ Moderate[b]
Upper respiratory tract infection	3	546	0.92 (0.64 to 1.32)	0.644	0	⊕⊕◯◯ Low[a,b]
Urinary tract infection	3	546	0.80 (0.48 to 1.33)	0.387	0	⊕⊕◯◯ Low[b,c]
Varicella zoster virus infection	4	565	1.37 (0.76 to 2.48)	0.301	0	⊕⊕◯◯ Low[b,c]

Leucopenia	3	484	0.33 (0.10 to 1.13)	0.078	30.7	⨁⨁◯◯ Low[b,c]
Menstrual disorder	3	438	0.38 (0.17 to 0.87)	0.022*	0	⨁⨁⨁◯ Moderate[c]
Infusion-related AEs	3	820	1.08 (0.77 to 1.51)	0.651	22.3	⨁⨁◯◯ Low[b,c]

* significant P value < 0.05
[a] Downgraded (-1) for inconsistency: Substantial heterogeneity (I^2 >50%) was found among the trials.
[b] Downgraded (-1) for inconsistency: the 95% confidence intervals were wide, the study included no effect and failed to exclude important benefits or serious harmful effects.
[c] Downgraded (-1) for imprecision: Potential for small sample bias.

Anmerkung/Fazit der Autoren

The results of this meta-analysis provide further support for the notion that, compared with single-agent IT, a combination consisting of corticosteroids and doublet IT without biologics improved clinical outcomes in active proliferative LN. However, further studies are needed to identify the patients in whom C + doublet IT including biologics is most efficacious and to unify the definition of renal response to immunosuppressive treatments for LN.

Kommentare zum Review

In die systematische Übersichtsarbeit wurden Studien mit Kindern und Erwachsenen eingeschlossen.

Referenzen

6. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. J Am Soc Nephrol 2008;19:2001-2010.
7. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. Arthritis Rheum 2012;64:1215-1226.
25. Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med 2015;162:18-26.
26. Rovin BH, Solomons N, Pendergraft 3rd WF, Dooley MA, Tumlin J, Romero-Diaz J, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int 2019;95:219-231.
27. Sun J, Zhang H, Ji Y, Gui M, Yi B, Wang J, et al. Efficacy and safety of cyclophosphamide combined with mycophenolate mofetil for induction treatment of class IV lupus nephritis. Int J Clin Exp Med 2015;8:21572-21578.
28. Jayne D, Appel G, Chan T, Barkay H, Weiss R, Wofsy D. LB0003 a randomized controlled study of laquinimod in active lupus nephritis patients in combination with standard of care. Ann Rheum Dis 2013;72:A164.
29. Li EK, Tam LS, Zhu TY, Li M, Kwok CL, Li TK, et al. Is combination rituximab with cclophosphamide better than rituximab alone in the treatment of lupus nephritis? Rheumatology 2009;48:892-898.
30. Zhang J, Zhao Z, Hu X. Effect of rituximab on serum levels of anti-c1q and antineutrophil cytoplasmic autoantibodies in refractory severe lupus nephritis. Cell Biocehm Biophys 2015;72:197-201.
31. Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol 2014;66:379-389.
32. The ACCESS Trial Group. Treatment of lupus nephritis with abatacept: the abatacept and cyclophosphamide combination efficacy and safety study. Arthritis Rheumatol 2014;66:3096-3104.
33. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum 2013;65:2368-2379.

Deng J et al., 2018 [1].

Multitarget therapy versus intravenous cyclophosphamide in the induction treatment of lupus nephritis: a metaanalysis of randomized controlled trial

Zielsetzung

[…] to evaluate the efficacy and safety of multitarget therapy versus IVC as induction therapy in different LN pathological classes.

Methodik

Population:

patients who had been diagnosed with SLE according to the criteria of the American College or Rheumatology and biopsy-proven LN class III, IV, V, V+III, or V+IV according to the ISN/RPS 2003 classification

Intervention

TAC plus MMF

Komparator:

IVC

Endpunkte:

- complete renal remission
- change in urine protein
- change in serum albumin
- anti-dsDNA negative conversion rate
- serum C3 normalization rate
- adverse events

Recherche/Suchzeitraum:

[…] searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the China Biology Medicine Database (CBM), and the China National Knowledge Infrastructure Database (CNKI) (all to May 2017) […].

Qualitätsbewertung der Studien:

The quality of included studies was evaluated using the Cochrane Handbook.

Ergebnisse

Anzahl eingeschlossener Studien: (⇨ Anhang Tabelle 5)

- […] eight eligible citations (16-21,24,25) […] were included in the metaanalysis.
- In total, 406 patients were treated with multitarget therapy and 395 were treated with IVC.

Charakteristika der Population:

These eight studies involved a total of 801 patients, including 671 female patients.

Qualität der Studien:

- All of the included studies provided a statement regarding randomization; however, only four studies explained random sequence generation that was computer-generated (16,17,19,25).
- Four trials reported withdrawals and dropouts (16-19).
- The main study limitation was a failure to explain blinding or the lack of a double-blind design.

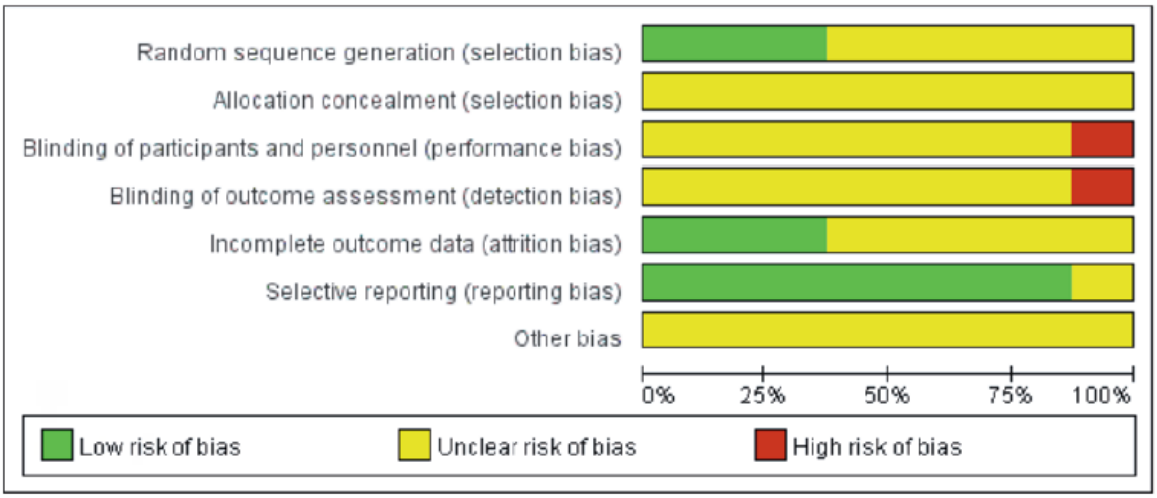

Abbildung 7: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Studienergebnisse:

The efficacy of multitarget therapy versus IVC for LN

The complete remission rate was reported in all eight trials. […] Based on the metaanalysis results, the complete remission rate of the multitarget group was significantly increased compared with the IVC group (RR: 1.94, 95% CI: 1.61-2.33; P < 0.00001). Subgroup analysis revealed that multitarget therapy was superior to IVC for including a complete remission of class IV LN (RR: 1.52, 95% CI: 1.10-2.08; P = 0.01) and class V LN (RR: 4.24, 95% CI: 1.30-13.88; P = 0.02) and significantly superior for class V+IV LN (RR: 2.29, 95% CI: 1.45-3.62; P = 0.0004); however, superiority was not observed for class III and class V+III LN.

Two trials reported the changes in urine protein and serum albumin after treatment. Multitarget therapy significantly reduced urine protein (MD: -1.07, 95% CI: -2.01 to -0.13; P = 0.03) and increased serum albumin (MD: 1.96, 95% CI: 0.63-3.29; P = 0.004) compared with IVC.

The anti-dsDNA negative conversion rates and serum C3 normalization rates were reported by four studies and one study, respectively. Based on the metaanalysis results, the anti-dsDNA negative conversion rate of the multitarget group was significantly increased compared with that of the IVC group (RR: 1.55, 95% CI: 1.06-2.26; P = 0.02) and only one group reported serum C3 normalization rates (RR: 1.31, 95% CI: 0.68-2.53; P = 0.43).

The safety of multitarget therapy versus IVC for LN

The metaanalysis results indicated that the rates of gastrointestinal symptoms, abnormal liver function, leukopenia, and irregular menstruation were significantly reduced in the multitarget therapy group compard with the IVC group. The rates of infection, alopecia, and hyperglycemia were similar between the two groups. However, the multitarget therapy group more frequently exhibited new onset hypertension compared with the IVC group.

Tabelle 2: Metaanalysis of adverse events

Outcomes	Studies	Multitarget therapy	IVC	Heterogeneity (P, I^2)	RR	95% CI	P-value
Gastrointestinal symptoms	7	42/376	82/365	0.05, 53%	0.51	0.37-0.71	<0.0001
Abnormal liver function	6	11/362	25/351	0.68, 0%	0.44	0.23-0.86	0.02
Leukopenia	7	11/376	34/365	0.31, 16%	0.33	0.18-0.63	0.0006

Infection	7	125/378	133/367	0.35, 10%	0.93	0.78-1.11	0.42
Irregular menstruation	5	6/279	18/265	0.84, 0%	0.36	0.16-0.84	0.02
Alopecia	5	11/332	21/321	0.78, 0%	0.52	0.26-1.05	0.07
Hyperglycemia	3	7/246	6/235	0.54, 0%	1.09	0.39-3.02	0.87
New-onset hypertension	5	23/304	6/293	0.88, 0%	3.14	1.40-7.04	0.006
RR < 1 favors multitarget therapy; RR > 1 favors IVC group							

Anmerkung/Fazit der Autoren

Our metaanalysis of current RCTs suggested that multitarget therapy is more effective than IVC for including a complete remission of LN; especially for class V+IV Chinese patients, and exhibits a better safety profile. Further large-scale high-quality RCTs are needed to confirm these results.

Kommentare zum Review

In die systematische Übersichtsarbeit wurden zum Teil Studien mit Jugendlichen und Erwachsenen eingeschlossen.

Alle Patientinnen und Patienten wurden mit Methylprednisolon als Impulstherapie gefolgt von Prednison p.o. behandelt.

Referenzen

16. Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med 2015;162:18-26.
17. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. J Am Soc Nephrol 2008;19:2001-2010.
18. Hu WX, Chen YH, Liu ZZ, Zhang HAT, Chen HP, Zeng CH, et al. A prospective clinical trial of corticosteroids in combination with mycophenolate mofetil dispersible tablets and tacrolimus for the induction treatment of lupus nephritis. Chin Nephrol Dail Transplant 2011;20:301-306.
19. Zhao WX, Xu H. Clinical efficacy and safety of lupus nephritis with multi-target therapy. Journal of Hebei Medical University in Chinese 2016;37:61-63.
20. Huang JP, Yu YZ, Gao W, Chen W, Hua DJ, Wu YZ, et al. Clinical study on the efficacy and safety of treatment of both proliferative and membranous lupus nephritis with multitarget therapy. Chin Clin Nephrol 2017;17:100-104.
21. Jang J, Guo Q, Duan R. Effects of mycophenolate mofetil combined with tacrolimus on immunological indexes and activity index of patients with lupus nephritis. J Clin Exp Med 2017;16:367-370.
24. Li M. Efficacy and safety of corticosteroids in combination with mycophenolate mofetil dispersible tablets and tacrolimus for the induction treatment of lupus nephritis. Chinese Journal of Clinical Rational Drug Use 2014;7:51-52.
25. Zhang Y, Lin SP, Chen DZ, Liang J. Clinical therapeutic effects of multi-target treatment on type-IV lupus nephritis and the effects on serum IL-6, IL-13, and IL-18 levels. Chin Clin Nephrol 2016;16:8-11.

3.3 Leitlinien

Fanouriakis A et al. 2020 [4]. + Kostopoulou M et al., 2020 [8].

EULAR

2019 Update of the Joint European League Against Rheumatism and European Renal Association– European Dialysis and Transplant Association (EULAR/ ERA–EDTA) recommendations for the management of lupus nephritis

Fragestellung

To update the 2012 EULAR/ERA–EDTA recommendations for the management of lupus nephritis (LN).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium
- Interessenskonflikte und mögliche finanzielle Abhängigkeiten dargelegt.
- Systematische Suche, Auswahl und Bewertung der Literatur
- Formale Konsensusprozesse, jedoch kein externes Begutachtungsverfahren dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist dargestellt
- Keine Informationen zur Überprüfung der Aktualität der Leitlinie.

Recherche/Suchzeitraum:

- PubMed: Since this is an update of the 2012 recommendations, we considered all English-language publications between January 2012 and December 2018.

LoE

- Risk of bias tool and Oxford Centre for Evidence-Based Medicine 2011

GoR

Oxford Centre for Evidence-Based Medicine 2011

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies; or extrapolations from level 1 studies
C	Level 4 studies; or extrapolations from level 2 or 3 studies
D	Level 5 evidence; or very inconsistent or inconclusive studies of any level

Empfehlungen

Erwachsene Patienten und Patientinnen

Recommendation/Statement		Level of agreement, mean (SD)
Initial treatment		
4.3 For patients with class III or IV (±V) LN, MMF(target dose: 2 to 3 g/day, or MPA at equivalent dose)	1a/A	9.84 (0.37)
or low-dose intravenous CY (500 mg every 2 weeks for a total of 6 doses)	1a/A	
in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio.		
4.4 Combination of MMF (target dose: 1 to 2 g/day, or MPA at equivalent dose) with a CNI (especially TAC) is an alternative, particularly in patients with nephrotic-range proteinuria.	1a/B	9.32 (0.93)
4.5 Patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as in 4.3–4.4,	2b/B	8.88 (1.56)
but high-dose ntravenous CY (0.5–0.75 g/m^2 monthly for 6 months) can also be considered.	1a/B	
4.6 To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months.	2b/C	9.48 (0.90)
4.7 In pure class V nephritis, MMF (target dose 2 to 3 g/day; or MPA at equivalent dose),	2a/B	
in combination with pulse intravenous methylprednisolone (total dose 500–2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by 3 months)	2b/C	9.28 (0.96)
is recommended as initial treatment due to best efficacy/toxicity ratio.		
4.8 Alternative options for class V nephritis include intravenous CY,	2b/B	9.28 (0.92)
or CNIs (especially TAC) in monotherapy	2b/B	
or in combination with MMF/MPA, particularly in patients with nephrotic-range proteinuria.	1b/B	
4.9 HCQ should be coadministered,	2a/B	9.28 (1.40)
at a dose not to exceed 5 mg/kg/day and adjusted for the GFR.	3b/C	
Subsequent treatment		
4.10 If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF/MPA (dose: 1 to 2 g/day)—especially if it was used as initial treatment—	1a/A	9.80 (0.49)
or AZA (2 mg/kg/day)—preferred if pregnancy is contemplated—in combination with low-dose prednisone (2.5–5 mg/day) when needed to control disease activity.	1a/A	
4.11 Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years therapy in *complete clinical response*. HCQ should be continued long-term.	2b/C	9.40 (0.75)
Non-responding/refractory disease		
4.13 In case of failure to achieve the treatment goals, thorough evaluation of the possible causes is recommended, including assessment of adherence to treatment and therapeutic drug monitoring.	5/D	9.84 (0.46)
4.14 For active non-responding/refractory disease, treatment may be switched to one of the alternative initial therapies mentioned above,	2b/B–C	9.64 (0.62)
or RTX (1000 mg on days 0 and 14) may be given.	2b/C	
5.6 Belimumab may be considered as add-on treatment, to facilitate glucocorticoid sparing, control extra-renal lupus activity and decrease the risk for extra-renal flares.	2a/C	8.48 (1.92)

Level of agreement (LoA) for each statement on a 0–10 rating scale (10 being full agreement),

Hydroxychloroquine in lupus nephritis

3.1 Association of HCQ use with risk for LN, baseline parameters and short-term outcomes

Outcome	Evidence and example(s) of effect size	Study design *(best, if > 1 study)*	References
Renal involvement in SLE	HCQ may be associated with lower occurrence of LN in SLE patients (OR 0.38-0.58 in 2 studies) – one study showed no such association	4	[40,76,77]
Kidney histology	HCQ has been associated with lower risk for tubulointerstitial inflammation on kidney bx (OR 0.27)	5	[78]
Response to treatment	HCQ use may be associated with complete response at 1st year (one study, only in univariable analysis)	5	[24]
Risk for infections	HCQ use may be associated with lower risk for infections (HR 0.78 in one study, only in univariable analysis)	5	[79]

3.1 Association of HCQ use with long-term outcomes

Outcome	Evidence and example(s) of effect size	Study design *(best, if > 1 study)*	References
ESRD	HCQ use associated with reduced risk for ESRD/CKD or doubling of SCr (adj. HR 0.18-0.40) • *Post-hoc analysis of ALMS RCT (n=370):* Lack of treatment with antimalarials had OR=2.4 for treatment failure (death or ESRD or sustained SCr doubling or renal flare or requirement for rescue therapy) during maintenance phase	2	[40,62,80–83]
Renal flares	Equivocal data regarding protection from renal flares with HCQ use (1 positive + 1 negative study – 1 study showing lower [HCQ] in patients who flared)	5	[84–86]
Mortality	HCQ use associated with reduced risk for death (OR 0.24-0.58)	5	[87,88]

CYC vs. MMF for induction therapy in LN (comparative studies)#

Outcome	Summary of evidence	Study design *(best)*	Reference
Short-term efficacy	At 6-12 months follow up, comparable efficacy between treatments in terms of remission (CR, PR and CR/PR) (Response rates: CYC 31%-87% MMF 33%-81%)	1	[61,89–110]
	Meta-analysis of 8 trials (n=828) with a median follow-up of 12mo: RR for MMF vs CYC: CR:1.17 (p=ns), PR: 1.02 (p=ns)	1	[111]
Safety	MMF has been associated with lower risk for ovarian failure and leucopenia, but more GI symptoms In one meta-analysis of 725 patients (7 trials), f-u 6months: RR for MMF vs. CYC: Infections: 0.72 (p=ns), Leukopenia: RR 0.47, Ovarian failure/amenorrhea: RR 0.14, Diarrhea and GI symptoms: RR 2.54	1	[59,61,89,91–101,103,104,106,108,110,111,113–115]
Long-term efficacy	Single RCT (ALMS) followed for 36mo: lower rates of treatment failure in CYC arm (OR 0.5)	2 (n=370)	[82]
	Retrospective studies with follow up >3 years indicate that both induction therapy have similar long-term outcomes (CKD, eGFR, SDI, renal relapse)	5	[112,115–117]
	Repeated kidney biopsies in a cohort of 25 patients with quiescent disease and a f-u >42 months showed a superior effect of CYC on activity index but not on chronicity index	5 (n=25)	[116]
	Single retrospective study reported 10-year renal survival favoring MMF, in patients with ANCA-positive LN (MMF vs. CYC (100% vs. 78.4) p=0.039)	5 (n=49)	[99]

Q5.'Maintenance' therapies in lupus nephritis? (including dosage of glucocorticoids, and use of CNIs)

5.2.1 MMF vs. AZA for maintenance therapy of LN (comparative)

Outcome	Summary of evidence	Study design *(best)*	Reference
Relapses	Trend for a more favorable effect of MMF compared to AZA F-u range: 1 - 10 years - Risk of renal relapse significantly greater in AZA (RR 1.83)	1	[86,93,98,111,112]
Renal parameters	Similar risk of ESRD (RR 0.45) and doubling of SCr (RR 0.52) between MMF and AZA, p=ns for both	1	[98,102,111,136,164–166]
Mortality	Comparable risk of mortality (RR 0.58) between MMF and AZA	1	[98,111,136]

10.3.3 Efficacy of other agents in LN

Drug	Summary of evidence	Study design *(best)*	Sample	Reference
Belimumab	Antiproteinuric effect and fewer renal flares (1.5% vs. 4.9% in the BLISS post-hoc analysis) in a mixed new-onset/refractory population	2 (post-hoc data of BLISS		[246,247]
	In a subgroup analysis of an RCT (Belimumab+soc vs placebo+soc) proteinuria was reduced in 54.5% in the belimumab group compared to 25.0% in the placebo group	4	39	[248–250]

Pädiatrische Patienten und Patientinnen

Recommendation/Statement		Level of agreement, mean (SD)
10.Management of paediatric patients		
10.1 LN in children is more common at presentation and more severe with increased damage accrual; the diagnosis, management and monitoring are similar to that of adults.	**3b/C**	**9.68 (0.68)**
10.2 A coordinated transition programme to adult specialists is essential to ensure adherence to therapy and optimisation of long-term outcomes.	**5/D**	**9.84 (0.37)**

Kidney involvement is more common in childhood compared with adult-onset SLE, often as a presenting manifestation, while renal flares are observed in more than 50% of patients.120 121 Since the 2012 EULAR/ERA—EDTA recommendations, American and European groups of experts in paediatric SLE and LN have published recommendations for the management of childhood-onset LN; both are largely based on data extrapolation from the studies in adults.122 123 Notwithstanding differences between children and adults, the respective statements from the 2012 recommendations remained unchanged; diagnosis, treatment) and monitoring should follow the same principles as in adult disease. For children in adolescence, a transition programme is recommended to ensure adherence and optimal outcomes.

120 Elmougy A , Sarhan A , Hammad A , et al . Lupus nephritis in Egyptian children: a 16-year experience. J Nephrol 2015;28:557–62.doi:10.1007/s40620-014-0157-x pmid:http://www.ncbi.nlm.nih.gov/pubmed/25491938 PubMedGoogle Scholar
121.↵ Fiorot FJ , Islabão AG , Pereira RM , et al . Disease presentation of 1312 childhood-onset systemic lupus erythematosus: influence of ethnicity. Clin Rheumatol 2019;38:2857–63.doi:10.1007/s10067-019-04631-0 pmid:http://www.ncbi.nlm.nih.gov/pubmed/31209708 PubMedGoogle Scholar
122.↵ Groot N , de Graeff N , Marks SD , et al . European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. Ann Rheum Dis 2017;76:1965–73.doi:10.1136/annrheumdis-2017-211898 pmid:http://www.ncbi.nlm.nih.gov/pubmed/28877866 Abstract/FREE Full TextGoogle Scholar
123.↵ Mina R , von Scheven E , Ardoin SP , et al . Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. Arthritis Care Res 2012;64:375–83.doi:10.1002/acr.21558 pmid:http://www.ncbi.nlm.nih.gov/pubmed/22162255 CrossRefPubMedWeb of ScienceGoogle Scholar

---

Groot N et al., 2017 [6] + Smith et al. 2019 [10]

European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative

Zielsetzung/Fragestellung

To provide guidance regarding best practices for the diagnosis and management of paediatric rheumatic diseases.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium
- Interessenskonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz jedoch nur nach Evidenztyp
- Formale Konsensusprozesse, jedoch kein externes Begutachtungsverfahren dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt
- Keine Angaben zur Überprüfung der Aktualität der Leitlinie

Recherche/Suchzeitraum:

- PubMed/MEDLINE, EMBASE and Cochrane databases in July 2013

LoE

Supplementary Table 3: Level of evidence (26, 27)

	For diagnostic/observational studies	For treatment studies
1A	Meta-analysis of cohort studies	Meta-analysis of randomised controlled trials
1B	Meta-analysis of case-control studies	Randomised controlled trial
2A	Cohort studies	Controlled study without randomisation
2B	Case-control studies	Quasi-experimental study
3	Non-comparative descriptive studies	Descriptive study
4	Expert opinion	Expert opinion

GoR

Supplementary Table 4: Strength of recommendations (22)

A	Based on level 1 evidence
B	Based on level 2 evidence or extrapolated from level 1 evidence
C	Based on level 3 evidence or extrapolated from level 1 or 2 evidence
D	Based on level 4 evidence or extrapolated from level 3 or 4 evidence

Empfehlungen

	Level of evidence	Strength	Agreement (%)
Treatment recommendations			
1. All children with lupus should be on hydroxychloroquine routinely.	2A	B	100
2. In all decisions of treatment change or modification, compliance should be actively checked.	3	C	100
3. When it is not possible to taper the prednisone dose, a DMARD should be added to the therapy.	3	C	100
4. Mild/moderate haematological involvement: when haemolysis is present and Hb is lower than normal, a DMARD should be added to the therapy.	3	C	100
5. If rituximab is required, the recommended dose is either 750 mg/m^2/dose (up to a maximum of 1 g) at day 1 and day 15, or 375 mg/m^2/dose once a week for four doses.	3	C	100

General treatment recommendations

It is recommended that all children with lupus should be on HCQ routinely. A systematic review of 95 articles analysing the beneficial and adverse effects of antimalarial therapies such as HCQ in adults with SLE showed a broad spectrum of beneficial effects, such as a higher remission rate, less relapses and less accrual of damage. Additionally, HCQ has a favourable safety profile.89 Adult studies show that long-term use of HCQ is relatively safe, although the risk of retinopathy increases with the increasing cumulative dose.89 Unfortunately, no such evidence is available for children with cSLE, but studies in patients with juvenile idiopathic arthritis show that doses up to 6 mg/kg/day (based on lean body weight) are safe to use.90

When a patient experiences side effects from a drug, choice of therapy will need to be reassessed and switched if necessary. If disease severity is such that tapering of oral prednisolone is not possible despite adequate compliance to oral prednisone and HCQ, addition of a disease-modifying antirheumatic drug (DMARD) is recommended to improve disease control and permit subsequent corticosteroid tapering. Examples of DMARDs often used include mycophenolate mofetil, azathioprine, methotrexate or cyclophosphamide in severe cases.

The use of rituximab has been described in six studies including a total of 115 individual patients with cSLE. All patients had acute, life-threatening symptoms or symptoms that did not respond to standard treatment. Two dose regimens were described, which both proved to be effective and safe in the majority of the patients.95–100

89 Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, et al. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis 2010;69:20–8.
90 Ziering CL, Rabinowitz LG, Esterly NB. Antimalarials for children: indications, toxicities, and guidelines. J Am Acad Dermatol 1993;28(5 Pt 1):764–70.
95 Willems M, Haddad E, Niaudet P, et al. Rituximab therapy for childhood-onset systemic lupus erythematosus. J Pediatr 2006;148:623–7.
96 Polido-Pereira J, Ferreira D, Rodrigues AM, et al. Rituximab use in pediatric autoimmune diseases: four case reports. Ann N Y Acad Sci 2009;1173:712–20.
97 Podolskaya A, Stadermann M, Pilkington C, et al. B cell depletion therapy for 19 patients with refractory systemic lupus erythematosus. Arch Dis Child 2008;93:401–6.
98 Nwobi O, Abitbol CL, Chandar J, et al. Rituximab therapy for juvenile-onset systemic lupus erythematosus. Pediatr Nephrol 2008;23:413–9.
99 Marks SD, Patey S, Brogan PA, et al. B lymphocyte depletion therapy in children with refractory systemic lupus erythematosus. Arthritis Rheum 2005;52:3168–74.
100 Watson L, Beresford MW, Maynes C, et al. The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE. Lupus 2015;24:10–17.

Treatment recommendation

The evidence for the treatment of NP- Childhood-onset systemic lupus erythematosus (cSLE) in children is especially limited. Recommendations are therefore based principally on adult recommendations for the management of NP-SLE,123 adapted for use in children by the expert panel. […] When non-SLE-related

causes for neuropsychiatric symptoms or signs are excluded, corticosteroids and immunosuppressive therapy are indicated.123

123 Bertsias GK, Ioannidis JP, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010;69:2074–8

Fanouriakis A et al., 2019 [3].

EULAR

2019 update of the EULAR recommendations for the management of systemic lupus erythematosus.

Fragestellung

Our objective was to update the EULAR recommendations for the management of systemic lupus erythematosus (SLE), based on emerging new evidence

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt
- Systematische Suche und Auswahl der Literatur
- Bewertung der Evidenz: „Evidence was categorised based on the design and validity of available studies"; es ist unklar, ob und welches formales Bewertungsinstrument zur Einschätzung der Validität der Studien verwendet wurde
- Formale Konsensusprozesse, aber externes Begutachtungsverfahren nicht dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist dargestellt;
- Regelmäßige Überprüfung der Aktualität: The guideline will be reviewed in 5 years' time.

Recherche/Suchzeitraum:

- from 01/2007 until 12/2017, with two exceptions: (1) treatment of skin disease, where an unrestricted date search was performed and (2) renal disease, where search was limited to the period 01/2012–12/2017 (since the EULAR recommendations for LN were published in 2012).

LoE

- Oxford Centre for Evidence-Based Medicine 2011

GoR

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies; or extrapolations from level 1 studies
C	Level 4 studies; or extrapolations from level 2 or 3 studies
D	Level 5 evidence; or very inconsistent or inconclusive studies of any level

Empfehlungen

Recommendations for the management of patients with systemic lupus erythematosus (mit Fokus: Renal disease)

Recommendation/Statement	Level of agreement, mean (SD)
1. Goals of treatment	
1.1 Treatment in SLE should aim at remission or low disease activity (**2b/B**) and prevention of flares (**2b/B**) in all organs, maintained with the lowest possible dose of glucocorticoids.	10.0 (0)
1.2 Flares of SLE can be treated according to the severity of organ(s) involvement by adjusting ongoing therapies (glucocorticoids, immunomodulating agents) to higher doses, switching or adding new therapies (**2b/C**).	9.95 (0.22)
2. Treatment of SLE	
2.1 HCQ	
2.1.1 HCQ is recommended for all patients with SLE (**1b/A**), unless contraindicated, at a dose not exceeding 5 mg/kg/real BW (**3b/C**).	9.65 (1.11)
2.1.2 In the absence of risk factors for retinal toxicity, ophthalmological screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter (**2b/B**).	9.75 (0.70)
2.2 GC	
2.2.1 GC can be used at doses and route of administration that depend on the type and severity of organ involvement (**2b/C**).	9.95 (0.22)
2.2.2 Pulses of intravenous methylprednisolone (usually 250–1000 mg per day, for 1–3 days) provide immediate therapeutic effect and enable the use of lower starting dose of oral GC (**3b/C**).	9.85 (0.36)
2.2.3 For chronic maintenance treatment, GC should be minimised to less than 7.5 mg/day (prednisone equivalent) (**1b/B**) and, when possible, withdrawn.	9.65 (0.65)
2.2.4 Prompt initiation of immunomodulatory agents can expedite the tapering/discontinuation of GC (**2b/B**).	9.90 (0.30)
2.3 Immunosuppressive therapies	
2.3.1 In patients not responding to HCQ (alone or in combination with GC) or patients unable to reduce GC below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as *methotrexate*, (**1b/B**) *azathioprine* (**2b/C**) or *mycophenolate* (**2a/B**) should be considered.	9.85 (0.48)
2.3.2 Immunomodulating/immunosuppressive agents can be included in the initial therapy in cases of organ-threatening disease (**2b/C**).	9.85 (0.48)
2.3.3 *Cyclophosphamide* can be used for severe organ-threatening or life-threatening SLE as well as 'rescue' therapy in patients not responding to other immunosuppressive agents (**2b/C**).	9.90 (0.30)
2.4 Biologics	
2.4.1 In patients with inadequate response to standard-of-care (combinations of HCQ and GC with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses, add-on treatment with *belimumab* should be considered (**1a/A**).	9.20 (0.81)
2.4.2 In organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents, *rituximab* can be considered (**2b/C**).	9.85 (0.48)
3.4 Renal disease	
3.4.1 Early recognition of signs of renal involvement and—when present—performance of a diagnostic renal biopsy are essential to ensure optimal outcomes (2b/B).	9.95 (0.22)
3.4.2 *Mycophenolate* (**1a/A**) or *low-dose intravenous cyclophosphamide* (**2a/B**) are recommended as initial (induction) treatment, as they have the best efficacy/toxicity ratio.	9.85 (0.36)
3.4.3 In patients at high risk for renal failure (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis], similar regimens may be considered but high-dose intravenous cyclophosphamide can also be used (**1b/A**).	9.45 (0.80)
3.4.4 For maintenance therapy, *mycophenolate* (**1a/A**) or *azathioprine* (**1a/A**) should be used.	9.75 (0.62)
3.4.5 In cases with stable/improved renal function but *incomplete renal response* (persistent proteinuria >0.8–1 g/24 hours after at least 1 year of immunosuppressive treatment), *repeat biopsy* can distinguish chronic from active kidney lesions (**4/C**).	9.85 (0.48)
3.4.6 Mycophenolate may be combined with low dose of a calcineurin inhibitor in severe nephrotic syndrome (**2b/C**) or incomplete renal response (**4/C**), in the absence of uncontrolled hypertension, high chronicity index at kidney biopsy and/or reduced GFR.	9.50 (0.81)

Continued

Renal disease

Patients at high risk of developing renal involvement (males, juvenile lupus onset, serologically active including positivity for anti-C1q antibodies)[113–115] should be under vigilant monitoring (eg, at least every 3 months) to detect early signs of kidney disease. Following diagnosis, secured with a kidney biopsy, treatment of LN includes an initial induction phase, followed by a more prolonged maintenance phase. MMF and CYC are the IS agents of choice for induction treatment; low-dose CYC (Euro-Lupus regimen, online supplementary table 5) is preferred over highdose CYC as it has comparable efficacy and lower risk of gonadotoxicity. [57 116 117] Published data support the use of MMF and high-dose CYC (online supplementary table 5) in severe forms of LN associated with increased risk of progression into end-stage renal disease (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis).[118 119] An early significant drop in UPr (to ≤1 g/day at 6 months or ≤0.8 g/day at 12 months) is a predictor of favourable long-term renal outcome.[21 117 120] MMF or AZA may be used as maintenance therapy, with the former associated with fewer relapses;[121 122] the choice depends on the agent used for induction phase and on patient characteristics, including age, race and wish for pregnancy. In refractory or relapsing disease, RTX may be considered. Following the EULAR recommendations for LN in 2012, several studies have been published regarding the use of CNIs to treat proliferative LN, either alone or in the form of a 'multitarget therapy' (combination of tacrolimus with MMF).[123–127] These studies were performed almost exclusively in Asian populations and had short follow-up; hence, data have to be corroborated with longer duration studies in multiethnic populations. To this end, at present, CNIs may be considered as second-line agents for induction or maintenance therapy mainly in membranous LN, podocytopathy, or in proliferative disease with refractory nephrotic syndrome,

despite standard-of-care within 3–6 months;[128] [129] in the latter case, they may be used alone or in combination with MMF, since small, observational studies have shown the CNI/MMF combination to be effective in disease refractory to standard therapy.[130–132] Monitoring SCr and blood levels of CNI to avoid chronic drug toxicity is essential.

Referenzen:

21 Dall'Era M, Cisternas MG, Smilek DE, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus nephritis cohort. Arthritis Rheumatol 2015;67:1305–13.
57 Tamirou F, Husson SN, Gruson D, et al. Brief report: the Euro-Lupus low-dose intravenous cyclophosphamide regimen does not impact the ovarian reserve, as measured by serum levels of anti-müllerian hormone. Arthritis Rheumatol 2017;69:1267–71. 2017;69:1267–71.
113 Artim-Esen B, Çene E, Şahinkaya Y, et al. Cluster analysis of autoantibodies in 852 patients with systemic lupus erythematosus from a single center. J Rheumatol 2014;41:1304–10.
114 Duarte-García A, Barr E, Magder LS, et al. Predictors of incident proteinuria amongpatients with SLE. Lupus Sci Med 2017;4:e000200.
115 Tang X, Huang Y, Deng W, et al. Clinical and serologic correlations and autoantibody clusters in systemic lupus erythematosus: a retrospective review of 917 patients in South China. Medicine 2010;89:62–7.
116 Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus nephritis trial, a randomized trial of low-dose versus highdose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.
117 Houssiau FA, Vasconcelos C, D'Cruz D, et al. The 10-year follow-up data of the Euro-Lupus nephritis trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis 2010;69:61–4.
120 Houssiau FA, Vasconcelos C, D'Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from longterm followup of patients in the Euro-Lupus nephritis trial. Arthritis Rheum 2004;50:3934–40.
121 Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365:1886–95.
122 Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the maintain nephritis trial. Ann Rheum Dis 2010;69:2083–9.
123 Chen W, Tang X, Liu Q, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. Am J Kidney Dis 2011;57:235–44.
124 Lee YH, Lee HS, Choi SJ, et al. Efficacy and safety of tacrolimus therapy for lupus nephritis: a systematic review of clinical trials. Lupus 2011;20:636–40.
125 Miyasaka N, Kawai S, Hashimoto H. Efficacy and safety of tacrolimus for lupus nephritis: a placebo-controlled double-blind multicenter study. Mod Rheumatol 2009;19:606–15.
126 Bao H, Liu Z-H, Xie H-L, et al. Successful treatment of class V+IV lupus nephritis with multitarget therapy. J Am Soc Nephrol 2008;19:2001–10.
127 Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med 2015;162:18–26.
128 Szeto C-C, Kwan BC-H, Lai FM-M, et al. Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. Rheumatology 2008;47:1678–81.
129 Uchino A, Tsukamoto H, Nakashima H, et al. Tacrolimus is effective for lupus nephritis patients with persistent proteinuria. Clin Exp Rheumatol 2010;28:6–12.
130 Ikeuchi H, Hiromura K, Takahashi S, et al. Efficacy and safety of multi-target therapy using a combination of tacrolimus, mycophenolate mofetil and a steroid in patients with active lupus nephritis. Mod Rheumatol 2014;24:618–25.
131 Kasitanon N, Boripatkosol P, Louthrenoo W. Response to combination of mycophenolate mofetil, cyclosporin A and corticosteroid treatment in lupus nephritis patients with persistent proteinuria. Int J Rheum Dis 2018;21:200–7.
132 Mok CC, To CH, Yu KL, et al. Combined low-dose mycophenolate mofetil and tacrolimus for lupus nephritis with suboptimal response to standard therapy: a 12-month prospective study. Lupus 2013;22:1135–41

Gordon C et al., 2018 [5].

The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults

Leitlinienorganisation/Fragestellung

The aim of this guideline was to produce recommendations for the management of adult lupus patients in the UK that cover the diagnosis, assessment and monitoring of lupus and the treatment of mild, moderate and severe active lupus disease, but which do not imply a legal obligation.

Methodik

Grundlage der Leitlinie:

- Repräsentatives Gremium
- Interessenkonflikte dargelegt, einige Autoren erhielten von Pharmaunternehmen Honorare, Forschungsgelder
- Systematische Suche, Auswahl und Bewertung der Evidenz
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt
- Regelmäßige Überprüfung der Aktualität: The guideline will be reviewed in 5 years' time.

Recherche/Suchzeitraum:

- up to June 2015 (kein Fokus lupus nephritis)

LoE/GoR:

- The recommendations were developed in line with the BSR's Guidelines Protocol, using RCP, SIGN and AGREE II methodology to assess the level of evidence (LOE) and grade of recommendation (GOR).

Sonstige methodische Hinweise

- Focus of the literature review was on non-renal disease, as the EULAR/ERA-EDTA recommendations for LN were published [24] close to the time that we started work on this guideline.
- guideline development group recommended that patients with LN are managed according to the EULAR/ERA-EDTA recommendations for LN [24] and provide their strengths of agreement (SOAs) with a summary of the most important items in those recommendations

→Die Empfehlungen zu LN in dieser LL basieren nicht auf einer aktuellen Evidenzbasierung; sondern entsprechen den Empfehlungen der EULAR/ERA-EDTA zu LN aus dem Jahr 2012. Diese wurde aktualisiert (siehe Fanouriakis A et al., 2020)

Empfehlungen

Strength of agreement with key points of the EULAR/ ERA-EDTA **recommendations for the management of LN** [24] (Table 3)

Referenzen:
24 Bertsias GK, Tektonidou M, Amoura Z et al. Joint European League Against Rheumatism and European Renal Association European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771-82.

TABLE 3 Strength of agreement of authors with the main EULAR/ERA-EDTA recommendations for the management of LN

Management of SLE patients with renal involvement	SOA[a]
Assessment of renal involvement	
1. Indications for first renal biopsy in SLE Any sign of renal involvement—in particular, urinary findings such as reproducible proteinuria ⩾0.5 g/24 h, especially with glomerular haematuria and/or cellular casts—should be an indication for renal biopsy. Renal biopsy is indispensable since, in most cases, clinical, serologic and laboratory tests cannot accurately predict renal biopsy findings.	97
2. Pathological assessment of kidney biopsy The use of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system is recommended, with assessment not only of active and chronic glomerular and tubulointerstitial changes, but also of vascular lesions associated with aPLs/APS.	98
Treatment of renal involvement	
3. Indications and goals of immunosuppressive treatment in LN	98
3.1 Initiation of immunosuppressive treatment should be guided by a diagnostic renal biopsy. Immunosuppressive agents are recommended in class III_A or $III_{A/C}$ (±V) and IV_A or $IV_{A/C}$ (±V) nephritis, and also in pure class V nephritis if proteinuria exceeds 1 g/24 h despite the optimal use of renin–angiotensin–aldosterone system blockers.	
3.2 The ultimate goals of treatment in LN are long-term preservation of renal function, prevention of disease flares, avoidance of treatment-related harms and improved quality of life and survival. Treatment should aim for complete renal response with UPCR <50 mg/mol and normal or near-normal (within 10% of normal GFR if previously abnormal) renal function. Partial renal response, defined as ⩾ 50% reduction in proteinuria to subnephrotic levels and normal or near-normal renal function, should be achieved preferably by 6 months but no later than 12 months following initiation of treatment.	98
4. **Treatment of adult LN—initial treatment**	
4.1 For patients with class III_A or $III_{A/C}$ (±V) and class IV_A or $IV_{A/C}$ (±V) LN, mycophenolic acid (MPA) (MMF target dose: 3 g/day for 6 months, or MPA sodium at equivalent dose) or low-dose i.v. CYC (total dose 3 g over 3 months), in combination with glucocorticoids, are recommended as initial treatment as they have the best efficacy/toxicity ratio.	93
4.2 In patients with adverse prognostic factors (acute deterioration in renal function, substantial cellular crescents and/or fibrinoid necrosis), similar regimens may be used, but CYC can also be prescribed monthly at higher doses (0.75–1 g/m^2) for 6 months or orally (2–2.5 mg/kg/day) for 3 months.	92
4.3 To increase efficacy and reduce cumulative glucocorticoid doses, treatment regimens should be combined initially with three consecutive pulses of i.v. methylprednisolone 500–750 mg, followed by oral prednisone 0.5 mg/kg/day for 4 weeks, reducing to ⩽ 10 mg/day by 4–6 months	98
4.4 In pure class V nephritis with nephrotic-range proteinuria, MPA (MMF target dose 3 g/day for 6 months) in combination with oral prednisone (0.5 mg/kg/day) may be used as initial treatment based on better efficacy/toxicity ratio. CYC or calcineurin inhibitors (ciclosporin, tacrolimus) or rituximab are recommended as alternative options or for non-responders.	95
4.5 AZA (2 mg/kg/day) may be considered as an alternative to MPA or CYC in selected patients without adverse prognostic factors (as defined 4.2), or when these drugs are contraindicated, not tolerated or unavailable. AZA use is associated with a higher flare risk.	96
Subsequent treatment	
4.6 In patients improving after initial treatment, subsequent immunosuppression is recommended with either MPA at lower doses (initial target MMF dose 2 g/day) or AZA (2 mg/kg/day) for at least 3 years, in combination with low-dose prednisone (5–7.5 mg/day). Gradual drug withdrawal, glucocorticoids first, can then be attempted.	97
4.7 Patients who responded to initial treatment with MPA should remain on MPA unless pregnancy is contemplated, in which case they should switch to AZA at least 3 months prior to conception.	98
4.8 Calcineurin inhibitors can be considered in pure class V nephritis.	93
Refractory disease	
4.9 For patients who fail treatment with MPA or CYC, either because of lack of effect (as defined above) or due to adverse events, we recommend that the treatment is switched from MPA to CYC, or CYC to MPA, or that rituximab be given.	95
5. **Adjunct treatment in patients with LN**	
5.1 Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are indicated for patients with proteinuria (UPCR >50 mg/mmol) or hypertension.	98
6. **Management of end-stage renal disease in LN**	
6.1 All methods of renal replacement treatment can be used in lupus patients, but there may be increased risk of infections in peritoneal dialysis patients still on immunosuppressive agents, and vascular access thrombosis in patients with aPLs.	98
6.2 Transplantation should be performed when lupus activity has been absent, or at a low level, for at least 3–6 months, with superior results obtained with living donor and pre-emptive transplantation. aPLs should be sought during transplant preparation because they are associated with an increased risk of vascular events in the transplanted kidney.	96
7. **APS-associated nephropathy in SLE**	
7.1 In patients with lupus and APS-associated nephropathy (APSN), HCQ and/or antiplatelet/anticoagulant treatment should be considered.	91

[a]Reproduced from Bertsias *et al.* Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 71: 771–82. Copyright 2012, with permission from BMJ Publishing Group Ltd [24]. Numbers are mean (S.D.) and median (IQR) agreement level among authors. A score of 10 represents the highest SOA. GFR: glomerular filtration rate; SOA: strength of agreement; UPCR: urine protein:creatinine ratio.

Recommendations for the management of mild SLE

(i) Treatments to be considered for the management of mild non_organ-threatening disease include the disease-modifying drugs HCQ (1 ++/A) and MTX (1+/A), and short courses of NSAIDs (3/D) for symptomatic control. These drugs allow for the avoidance of or dose reduction of CSs (SOA 94%).

(ii) Prednisolone treatment at a low dose of ≤7.5 mg/day may be required for maintenance therapy (2+/C). Topical preparations may be used for cutaneous manifestations, and IA injections for arthritis (4/D) (SOA 93%).

(iii) High_Sun Protection Factor (SPF) UV-A and UV-B sunscreen are important in the management and prevention of UV radiation_induced skin lesions (2 ++/B). Patients must also be advised about sun avoidance and the use of protective clothing (4/D) (SOA 97%).

Recommendations for the management of moderate SLE

(i) The management of moderate SLE involves higher doses of prednisolone (up to 0.5 mg/kg/day) (2+/C), or the use of i.m. (4/D) or i.v. doses of methylprednisolone (MP) (2+/C). Immunosuppressive agents are often required to control active disease and are steroid-sparing agents (2+/C). They can also reduce the risk of long-term damage accrual (4/D) (SOA 98%).

(ii) MTX (1+/A), AZA (2+/C), MMF (2 ++/B), ciclosporin (2+/C) and other calcineurin inhibitors (3/D) should be considered in cases of arthritis, cutaneous disease, serositis, vasculitis or cytopaenias if HCQ is insufficient (SOA 97%).

(iii) For refractory cases, belimumab (1+/B) or rituximab (2+/C) may be considered (SOA 98%).

Recommendations for the management of severe SLE

(i) Patients who present with severe SLE, including renal and NP manifestations, need thorough investigation to exclude other aetiologies, including infection (4/D). Treatment is dependent on the underlying aetiology (inflammatory and/or thrombotic), and patients should be treated accordingly with immunosuppression and/or anticoagulation, respectively (4/D) (SOA 98%).

(ii) Immunosuppressive regimens for severe active SLE involve i.v. MP (2+/C) or high-dose oral prednisolone (up to 1 mg/kg/day) (4/D) to induce remission, either on their own or more often as part of a treatment protocol with another immunosuppressive drug (4/D) (SOA 98%).

(iii) MMF or CYC are used for most cases of LN and for refractory, severe non-renal disease (2++/B) (SOA98%).

(iv) Biologic therapies belimumab (1+/B) or rituximab (2+/C) may be considered, on a case-by-case basis, where patients have failed to respond to other immunosuppressive drugs, due to inefficacy or intolerance (SOA 98%).

(v) IVIG (2-/D) and plasmapheresis (3/D) may be considered in patients with refractory cytopaenias, thrombotic thrombocytopaenic purpura (TTP) (1+/B), rapidly deteriorating acute confusional state and the catastrophic variant of APS (SOA 93%).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2021) am 26.11.2021

#	Suchfrage
1	[mh “Lupus Erythematosus, Systemic”]
2	(lupus OR glomerulonephriti* OR SLE OR (libman NEXT sacks)):ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date from Nov 2016 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 26.11.2021

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	lupus erythematosus, systemic/therapy[mh]
2	((lupus[tiab]) AND ((((erythemato*[tiab]) OR sle[tiab]) OR nephriti*[tiab] OR nephropat*[tiab] OR kidney*[tiab] OR renal[tiab]) OR glomerulonephriti*[tiab]))
3	"libman sacks"[tiab]
4	#2 OR #3
5	(#4) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
6	#1 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR

#	Suchfrage
	handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	(#7) AND ("2016/11/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 26.11.2021

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	lupus erythematosus, systemic[mh]
2	((lupus[tiab]) AND ((((erythemato*[tiab]) OR sle[tiab]) OR nephriti*[tiab] OR nephropat*[tiab] OR kidney*[tiab] OR renal[tiab] OR systemic[tiab] OR disseminatus[tiab]) OR glomerulonephriti*[tiab]))
3	"libman sacks"[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2016/11/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 26.11.2021

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Deng J, Luo L, Zhu L, Xie H, xie H.** Multitarget therapy versus intravenous cyclophosphamide in the induction treatment of lupus nephritis: a metaanalysis of randomized controlled trials. Turk J Med Sci 2018;48(5):901-910.
2. **Deng J, Xie H, Zhu L, Luo L, Xie H.** Maintenance therapy for lupus nephritis with mycophenolate mofetil or azathioprine. A meta-analysis. Clin Nephrol 2019;91(3):172-179.
3. **Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al.** 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78(6):736-745.
4. **Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al.** 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis 2020;79(6):713-723.
5. **Gordon C, Amissah-Arthur MB, Gayed M, Brown S, Bruce IN, D'Cruz D, et al.** The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford) 2018;57(1):e1-e45.
6. **Groot N, de Graeff N, Avcin T, Bader-Meunier B, Brogan P, Dolezalova P, et al.** European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. Ann Rheum Dis 2017;76(11):1788-1796.
7. **Jiang YP, Zhao XX, Chen RR, Xu ZH, Wen CP, Yu J.** Comparative efficacy and safety of mycophenolate mofetil and cyclophosphamide in the induction treatment of lupus nephritis: a systematic review and meta-analysis. Medicine (Baltimore) 2020;99(38):e22328.
8. **Kostopoulou M, Fanouriakis A, Cheema K, Boletis J, Bertsias G, Jayne D, et al.** Management of lupus nephritis: a systematic literature review informing the 2019 update of the joint EULAR and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations. RMD Open 2020;6(2):e001263.
9. **Liu B, Ou Q, Tang Y, Fu S, Liang P, Yu Y, et al.** Corticosteroids combined with doublet or single-agent immunosuppressive therapy for active proliferative lupus nephritis. Clin Rheumatol 2019;38(9):2519-2528.
10. **Smith EMD, Sen ES, Pain CE.** Diagnosis and treatment of childhood-onset systemic lupus erythematosus (European evidence-based recommendations from the SHARE initiative). Arch Dis Child Educ Pract Ed 2019;104(5):259-264.
11. **Teng S, Tian Y, Luo N, Zheng Q, Shao M, Li L.** Efficacy and safety of an anti-CD20 monoclonal antibody, rituximab, for lupus nephritis: a meta-analysis [Online ahead of print]. Int J Rheum Dis 2021.
12. **Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, et al.** Immunosuppressive treatment for proliferative lupus nephritis. Cochrane Database of Systematic Reviews [online]. 2018(6):Cd002922. URL: http://dx.doi.org/10.1002/14651858.CD002922.pub4.

13. **Zhang H, Zhou M, Han X, Yang Y, Yu X.** Mycophenolate mofetil in the treatment of Chinese patients with lupus nephritis: a PRISMA-compliant meta-analysis. Medicine (Baltimore) 2020;99(33):e21121.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Anhang

Tabelle 1: Basic characteristics of the included randomized clinical trials (Liu B et al., 2019 [9]).

Study	Follow up (mo)	The type of LN	Regimen (drug dose)	No. of patients	Age (yr)	F (n)	Duration of LN	SCr (μmol/L)	Urinary protein (g/day)/UPCR (g/g)	SLE-DAI score	Anti-dsDNA positive (%)
AURA-LV Study [26]	6	Class III, IV, V, V + III/IV	C + VCS (39.5 mg bid) + MMF	88	30.6[a]	81	3.2[a] yr	-	4.48[a,d]	-	-
			C+ VCS (23.7 mg bid) + MMF	89	31.4[a]	76	4.2[a] yr	-	5.16[a,d]	-	-
			C + placebo + MMF	88	33.1[a]	73	3.5[a] yr	-	4.43[a,d]	-	-
Sun et al. [27]	6	Class IV	C + IVCY + MMF	42	31.9[a]	38	0.5-24 mo	128.0[a]	2.04[a,c]	14.1[a]	-
			C + IVCY	40	33.3[a]	37	0.5-24 mo	118.0[a]	2.45[a,c]	13.8[a]	-
Liu et al. [25]	6	Class III, IV, V, V + III/IV	C + MMF + tacrolimus	181	30.3[b]	168	2[b] mo	69.0[b]	3.44[b,c]	16.0[b]	59.2
			C + IVCY	181	33.6[b]	161	3[b] mo	72.5[b]	3.68[b,c]	15.0[b]	63.1
Zhang et al. [30]	12	Refractory Class V + III/IV	C + RTX + IVCY	42	38.7[a]	31	-	115.08[a]	4.82[a,c]	14.90[a]	-
			C + IVCY	42	39.1[a]	29	-	116.39[a]	4.91[a,c]	14.48[a]	-
The ACCESS Trial Group [32]	6	Class III, IV, V + III/IV	C + abatacept + (IVCY-AZA)	66	32.0[a]	58	Time from onset of LN <1 yr (n) 47	106.1[a]	3.8[a,c]	-	75
			C + placebo + (IVCY-AZA)	68	32.7[a]	64	Time from onset of LN <1 yr (n) 48	114.9[a]	4.5[a,c]	-	75
Furie et al. [31]	12	Class III, IV, V + III/IV	C + abatacept + (30/10)[e] + MMF	99	31.0[a]	84	-	79.6[b]	3.9[a,d]	-	-
			C + abatacept + (10/10)[f] + MMF	99	30.5[a]	86	-	70.7[b]	4.3[a,d]	-	-
			C + placebo + MMF	100	31.8[a]	81	-	70.7[b]	3.6[a,d]	-	-
Mysler et al. [33]	12	Class III, IV, V + III/IV	C + ocrelizumab (1000 mg) + (IVCY-AZA)/MMF	128	30.6[a]	110	0.7[b] yr	88.4[a]	2.9[b,d]	-	-
			C + ocrelizumab (400 mg) + (IVCY-AZA)/MMF	127	31.9[a]	115	0.8[b] yr	88.4[a]	3.0[b,d]	-	-
			C + placebo + (IVCY-AZA)/MMF	126	31.3[a]	107	0.6[b] yr	79.6[a]	2.7[b,d]	-	-
Jayne et al. [28]	6	Active	C + laquinimod + MMF	31	-	-	-	-	-	-	-
			C + placebo + MMF	15	-	-	-	-	-	-	-
Rovin et al. [7]	12	Class III, IV, V + III/IV	C + RTX + MMF	72	31.8[a]	63	11.1[b] mo	88.4[a]	3.8[a,d]	-	-
			C + placebo + MMF	72	29.4[a]	67	5.4[b] mo	88.4[a]	4.2[a,d]	-	-
Li et al. [29]	12	Class III, IV, V + III/IV	C + RTX + IVCY	10	39.6[a]	9	9.9[a] yr	134.8[a]	3.8[a,c]	10.3[a]	-
			C + RTX	9	40.3[a]	9	6.9[a] yr	99.8[a]	4.1[a,c]	8.5[a]	-
Bao et al. [6]	9	Class IV + V	C + MMF + tacrolimus	20	27.2[a]	16	30.0[b] mo	76.9[a]	4.41[a,c]	14.9[a]	60
			C + IVCY	20	30.6[a]	18	26.0[b] mo	78.7[a]	4.10[a,c]	14.0[a]	60

[a] Expressed as mean values
[b] Expressed as median values
[c] The values of urinary protein (g/day)
[d] The values of UPCR (g/g)
[e] Abatacept administered at 30 mg/kg on days 1, 15, 29, and 57 followed by abatacept administered at approximately 10 mg/kg on days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337
[f] Abatacept administered at approximately 10 mg/kg on all infusion days

Tabelle 2: Efficacies of the two treatments (Liu B et al., 2019 [9]).

Outcomes	No. of trials	No. of participants	Relative effect			GRADE
			Ratio (95% CI)	P value	I^2, %	
Complete response rate	10	1651	RR 1.40 (1.09 to 1.79)	< 0.01**	57	⊕⊕⊕○ Moderate[a]
Partial response rate	9	1386	RR 1.03 (0.87 to 1.23)	0.716	26.3	⊕⊕⊕○ Moderate[b]
Overall response rate	10	1432	RR 1.22 (1.09 to 1.35)	< 0.01**	30.5	⊕⊕⊕⊕ High
Change from baseline in SLE-DAI scores	2	446	SMD -0.49 (-0.68 to -0.30)	< 0.01**	19.9	⊕⊕⊕○ Moderate[c]
Negative conversion ratio of anti-dsDNA	4	437	RR 1.34 (1.06 to 1.69)	0.014*	0	⊕⊕⊕○ Moderate[c]

* Significant P value < 0.05
** Significant P value < 0.01
[a] Downgraded (-1) for inconsistency: substantial heterogeneity (I^2 > 50%) was found among the trials.
[b] Downgraded (-1) for inconsistency: the 95% confidence intervals were wide; the study included no effect and failed to exclude important benefits or serious harmful effects.
[c] Downgraded (-1) for imprecision: potential for small sample bias

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-406

Kontaktdaten

Deutsche Gesellschaft für Rheumatologie (DGRh)

Indikation gemäß Beratungsantrag

… ist in Kombination mit immunsuppressiven Basistherapien zur Behandlung von erwachsenen Patienten mit Lupusnephritis der Klasse III, IV oder V (einschließlich der gemischten Klassen III/V und IV/V) indiziert.

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Die hier beschriebene Indikation ist eindeutig, die angestrebte Intervention kann jedoch vielschichtig sein: a) es kann sich um jede Form der ergänzenden Therapie zur immunsuppressiven Therapie handeln, also z.B. Antihypertensiva, Lipidsenker oder auch Antikoagulantien; b) Immunmodulatoren wie z.B. Antimalariamittel oder Zytokininhibitoren oder c) weitere Immunsuppressiva soweit diese nicht als immunsuppressive Basistherapie bezeichnet werden.

Die Grundprinzipien der Behandlung der verschiedenen Formen der Lupusnephritis (LN) sind sehr gut in den EULAR Recommendations zur Lupusnephritis (1) zusammengefasst:
„Das Ziel der Therapie ist ein komplettes Ansprechen (Proteinurie <0,5-0,7gr/24h mit [nahezu] normaler glomerulärer Filtrationsrate) nach 12 Monaten; dieser Zeitraum kann bei Patienten mit Proteinurie im nephrotischen Bereich verlängert werden. Als Basisbehandlung jeder Form des systemischen Lupus erythematodes (SLE) ist Hydroxychloroquin empfohlen. Bei aktiver LN der Klassen III oder IV, incl. der Kombinationen mit V, wird eine Behandlung mit Mycophenolatmofetil (MMF 2-3g/Tag oder Mycophenolsäure (MPA) in äquivalenter Dosis) oder niedrig dosiertem intravenösem Cyclophosphamid (CY; 500mg x6 zweiwöchentliche Gaben) in Kombination mit Glukokortikoiden (Pulse von intravenösem Methylprednisolon, dann orales Prednison 0,3-0,5mg/kg/Tag) empfohlen. MMF/CNI (Calcineurin-Inhibitoren)-Kombination und hochdosiertes CY sind Alternativen bei Patienten mit Proteinurie im nephrotischen Bereich und ungünstigen prognostischen Faktoren. Als Erhaltungstherapien kommen MMF/MPA oder Azathioprin (AZA) in Frage.

Bei reinen Klasse-V-LN mit Proteinurie im nephrotischen Bereich oder Proteinurie >1g/24h trotz Renin-Angiotensin-Aldosteron-Blockade wird MMF in Kombination mit Glukokortikoiden bevorzugt. Zu den alternativen Optionen bei Nephritis der Klasse V gehören IV CY, CNI (Cyclosporin, Tacrolimus) als Monotherapie (2b/B) oder in Kombination mit MMF/MPA (1b/B), insbesondere bei Patienten mit Proteinurie im nephrotischen Bereich.

Die Beurteilung der Nieren, der extra-renalen Krankheitsaktivität und der Komorbiditäten erfolgt lebenslang. Bei unvollständigem Ansprechen oder nephritischen Schüben kann eine erneute Nierenbiopsie in Betracht gezogen werden. Bei terminalem Nierenversagen richtet sich die Immunsuppression nach den extra-renalen Manifestationen, wobei eine Transplantation gegenüber anderen Nierenersatzoptionen bevorzugt wird.

Bei nicht ansprechender Erkrankung wird ein Wechsel des Induktionsschemas oder Rituximab empfohlen.

In diesem Konzept sind MMF/MPA, CY, CNI, AZA und Glukokortikoide die Immunsuppressiva.

In Kombination zu dieser immunsuppressiven Basistherapie– das ist hier die Anfrage - werden Antimalariamittel und Renin-Angiotensin-Aldosteron-Blockade leitliniengemäß verwendet. Letztere sind bei UPCR >500 mg/g oder

Kontaktdaten

Deutsche Gesellschaft für Rheumatologie (DGRh)

Indikation gemäß Beratungsantrag

… ist in Kombination mit immunsuppressiven Basistherapien zur Behandlung von erwachsenen Patienten mit Lupusnephritis der Klasse III, IV oder V (einschließlich der gemischten Klassen III/V und IV/V) indiziert.

arterieller Hypertonie indiziert. Ergänzend werden Statine empfohlen abhängig vom Lipidlevel und erwarteten 10-Jahre Risiko für eine kardiovaskuläre Erkrankung, Knochen- und Impfschutz, Behandlung von Komorbiditäten. Eine Antikoagulation sollte bei einem nephrotischen Syndrom (Serumalbumin <20 g/L) oder Vorliegen von anti-Phospholipid Antikörpern erwogen werden.

Mittlerweile ist Benlysta in Kombination mit immunsuppressiver Basistherapie zur erweiterten Behandlung der LN zugelassen (2). Eine Einordnung in den Therapiealgorithmus der LN wird wohl erstmalig mit der deutschen Lupus Leitlinie erfolgen, die für Ende 2022 erwartet wird.

Die Versorgungspraxis des SLE in Deutschland ist partiell in der Kerndokumentation abgebildet, differenziert da aber nicht nach Organmanifestationen.

Bitte begründen Sie Ihre Ausführungen.

(hier ergänzen – sofern verfügbar – auf welcher (Daten-)Grundlage basiert die Einschätzung; ggf. beifügen der zitierten Quellen)

1 Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, Boletis J, Frangou E, Houssiau FA, Hollis J, Karras A, Marchiori F, Marks SD, Moroni G, Mosca M, Parodis I, Praga M, Schneider M, Smolen JS, Tesar V, Trachana M, van Vollenhoven RF, Voskuyl AE, Teng YKO, van Leew B, Bertsias G, Jayne D, Boumpas DT. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020 Jun;79(6):713-723. doi: 10.1136/annrheumdis-2020-216924. Epub 2020 Mar 27. PMID: 32220834.
2 Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, Amoura Z, Yu X, Mok CC, Santiago MB, Saxena A, Green Y, Ji B, Kleoudis C, Burriss SW, Barnett C, Roth DA. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180. PMID: 32937045.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Die Wahl des jeweiligen immunsuppressiven Basistherapeutikums hängt von der Rasse/Ethnizität, einer möglicherweise geplanten späteren Schwangerschaft, bestehenden Komorbiditäten, bekannten Unverträglichkeiten und dem Ansprechen auf Vortherapien ab. Aufgrund der sehr heterogenen Erkrankung gibt es hier keine Standards.

Bitte begründen Sie Ihre Ausführungen

(hier ergänzen – sofern verfügbar – auf welcher (Daten-)Grundlage basiert die Einschätzung; ggf. beifügen der zitierten Quellen)