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First Latin American clinical practice guidelines for the treatment of systemic lupus erythematosus: Latin American Group for the Study of Lupus (GLADEL, Grupo Latino Americano de Estudio del Lupus)–Pan-American League of Associations of Rheumatology (PANLAR)

Bernardo A Pons-Estel,[1] Eloisa Bonfa,[2] Enrique R Soriano,[3] Mario H Cardiel,[4] Ariel Izcovich,[5] Federico Popoff,[5] Juan M Criniti,[5] Gloria Vásquez,[6] Loreto Massardo,[7] Margarita Duarte,[8] Leonor A Barile-Fabris,[9] Mercedes A García,[10] Mary-Carmen Amigo,[11] Graciela Espada,[12] Luis J Catoggio,[3] Emilia Inoue Sato,[13] Roger A Levy,[14] Eduardo M Acevedo Vásquez,[15] Rosa Chacón-Díaz,[16] Claudio M Galarza-Maldonado,[17] Antonio J Iglesias Gamarra,[18] José Fernando Molina,[19] Oscar Neira,[20] Clóvis A Silva,[21] Andrea Vargas Peña,[22] José A Gómez-Puerta,[23] Marina Scolnik,[3] Guillermo J Pons-Estel,[1,24] Michelle R Ugolini-Lopes,[2] Verónica Savio,[25] Cristina Drenkard,[26] Alejandro J Alvarellos,[27] Manuel F Ugarte-Gil,[28,29] Alejandra Babini,[25] André Cavalcanti,[30] Fernanda Athayde Cardoso Linhares,[22] Maria Jezabel Haye Salinas,[27] Yurilis J Fuentes-Silva,[31] Ana Carolina Montandon de Oliveira e Silva,[32] Ruth M Eraso Garnica,[33] Sebastián Herrera Uribe,[34] Diana Gómez-Martín,[35] Ricardo Robaina Sevrini,[36] Rosana M Quintana,[1,24] Sergio Gordon,[37] Hilda Fragoso-Loyo,[35] Violeta Rosario,[38] Verónica Saurit,[27] Simone Appenzeller,[39] Edgard Torres dos Reis Neto,[13] Jorge Cieza,[40] Luis A González Naranjo,[6] Yelitza C González Bello,[41] María Victoria Collado,[42] Judith Sarano,[42] Soledad Retamozo,[27] María E Sattler,[43] Rocio V Gamboa-Cárdenas,[28] Ernesto Cairoli,[36] Silvana M Conti,[24] Luis M Amezcua-Guerra,[44] Luis H Silveira,[45] Eduardo F Borba,[2] Mariana A Pera,[10] Paula B Alba Moreyra,[46] Valeria Arturi,[10] Guillermo A Berbotto,[43] Cristian Gerling,[37] Carla A Gobbi,[46] Viviana L Gervasoni,[24] Hugo R Scherbarth,[37] João C Tavares Brenol,[47] Fernando Cavalcanti,[30] Lilian T Lavras Costallat,[39] Nilzio A Da Silva,[32] Odirlei A Monticielo,[47] Luciana Parente Costa Seguro,[2] Ricardo M Xavier,[47] Carolina Llanos,[48] Rubén A Montúfar Guardado,[49] Ignacio Garcia de la Torre,[50] Carlos Pineda,[51] Margarita Portela Hernández,[52] Alvaro Danza,[53] Marlene Guibert-Toledano,[54] Gil Llerena Reyes,[54] Maria Isabel Acosta Colman,[8] Alicia M Aquino,[8] Claudia S Mora-Trujillo,[40] Roberto Muñoz-Louis,[38] Ignacio García Valladares,[41] María Celeste Orozco,[55] Paula I Burgos,[48] Graciela V Betancur,[55] Graciela S Alarcón,[56,57] on behalf of the Grupo Latino Americano de Estudio del Lupus (GLADEL) and Pan-American League of Associations of Rheumatology (PANLAR)

Handling editor Josef S Smolen

For numbered affiliations see end of article.

Correspondence to
Dr Mario H Cardiel, Centro de Investigación Clínica de Morelia SC. Morelia, México; mhcardiel@hotmail.com

BAP-E, EB, ERS and MHC contributed equally.

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ABSTRACT

Systemic lupus erythematosus (SLE), a complex and heterogeneous autoimmune disease, represents a significant challenge for both diagnosis and treatment. Patients with SLE in Latin America face special problems that should be considered when therapeutic guidelines are developed. The objective of the study is to develop clinical practice guidelines for Latin American patients with lupus. Two independent teams (rheumatologists with experience in lupus management and methodologists) had an initial meeting in Panama City, Panama, in April 2016. They selected a list of questions for the clinical problems most commonly seen in Latin American patients with SLE. These were addressed with the best available evidence and summarised in a

standardised format following the Grading of Recommendations Assessment, Development and Evaluation approach. All preliminary findings were discussed in a second face-to-face meeting in Washington, DC, in November 2016. As a result, nine organ/system sections are presented with the main findings; an 'overarching' treatment approach was added. Special emphasis was made on regional implementation issues. Best pharmacologic options were examined for musculoskeletal, mucocutaneous, kidney, cardiac, pulmonary, neuropsychiatric, haematological manifestations and the antiphospholipid syndrome. The roles of main therapeutic options (ie, glucocorticoids, antimalarials, immunosuppressant agents, therapeutic plasma exchange, belimumab, rituximab, abatacept, low-dose aspirin and anticoagulants) were summarised in each section. In all cases, benefits and harms, certainty of the evidence, values and preferences, feasibility, acceptability and equity issues were considered to produce a recommendation with special focus on ethnic and socioeconomic aspects. Guidelines for Latin American patients with lupus have been developed and could be used in similar settings.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex multisystemic autoimmune disease resulting, oftentimes, in irreversible damage, diminished quality of life and reduced life expectancy.[1–3] Genetic and environmental factors play important roles in its pathogenesis.[4–8] Disease manifestations and severity vary according to the patients' racial/ethnic background and socioeconomic status (SES).[1 9 10] Data from *Grupo Latino Americano de Estudio del Lupus* (GLADEL), Lupus in Minorities: Nature vs Nurture (LUMINA) and the Lupus Family Registry and Repository cohorts have demonstrated that Latin American and North American Mestizo patients (mixed Amerindian and European ancestry), African descendants and Native Americans develop lupus earlier[11 12] although diagnostic delays may occur.[1] They also experience more severe disease, have higher disease activity levels,[1] accrue more organ damage[2] and have higher mortality rates,[1] succumbing mainly to disease activity and/or infections.[1 3 13–15]

Although guidelines for SLE treatment do exist and there is scarce evidence to support specific therapies for Latin American patients with lupus,[16–21] this regional effort has considered the impact of racial/ethnic background[1 10 22–28] and SES[3 9] on lupus outcomes and treatment response.[25 26] Other medication variables such as cost and availability were also taken into account since they affect adherence and are relevant in decision-making.[27 28] GLADEL and the Pan-American League of Associations of Rheumatology have joined efforts to produce these guidelines,[29] which are presented by organ systems, although manifestations usually occur in more than one. Nevertheless, treatment is usually tailored to the more severe manifestation(s), which usually benefits the less severe.

METHODS

Two working teams on logistics and methodological issues constituted by experienced Latin American rheumatologists and experts in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline system developed a framework for these guidelines. Nine organ/system sections were prepared with the main findings. Special emphasis was placed on reviewing local problems and regional publications.

The GRADE approach was followed in the process (http://www.gradeworkinggroup.org) answering the clinical questions voted most relevant by the panel. The description of the methodology followed to develop these guidelines has already been published.[29] All authors listed in this manuscript have participated in planning, drafting, reviewing, final approval and are accountable for all aspects of the manuscript. No ethical approval was required by institutions. We present the final recommendations and their supporting information. Comments from three patients with SLE were also considered.

Box 1 GLADEL–PANLAR Latin American guidelines for the treatment of systemic lupus erythematosus

Overarching principles

a. Treatment should be individualised, specialists and generalists should work together and the active involvement of patients and their family members on the overall therapeutic plan should be emphasised.
b. The therapeutic goal should be to reach and maintain remission or low-disease activity as soon as the diagnosis is made and for as long as possible.
c. Treatment should include photo-protection, osteoporosis, cardiovascular, metabolic syndrome and infection prevention, psychological support and pregnancy counselling.
d. All patients with lupus should receive AMs, except those who refuse them or who have absolute contraindications to take them.
e. GCs, if clinically needed, regardless of patient's disease manifestations, should be prescribed at the lowest possible dose and for the shortest period of time.

AM, antimalarials; GC, glucocorticoid; GLADEL, Grupo Latino Americano de Estudio del Lupus; PANLAR, Pan-American League of Associations of Rheumatology.

RESULTS

For each of the subheadings listed below, the panel considered interventions based on experience, availability, affordability and a stepwise therapeutic approach of the different alternatives. Standard of care (SOC) was defined as the use of hydroxychloroquine (HCQ) and, if clinically indicated, low-dose glucocorticoids (GC) (prednisone ≤7.5 mg or equivalent for the shortest time).[24] Chloroquine remains an alternative for some of the Latin American countries where HCQ is not available and careful monitoring of eye side effect is recommended. Overarching principles are shown in box 1. Tables summarising the evidence that was considered in the process are shown in online supplementary tables in https://doi.org/10.5061/dryad.bg8452h.

Musculoskeletal manifestations

a. Which is the best treatment for adult patients with SLE and musculoskeletal (MSK) manifestations?

Interventions considered

(1) SOC; (2) SOC plus methotrexate (MTX); (3) SOC plus leflunomide (LFN); (4) SOC plus belimumab; (5) SOC plus abatacept (ABT); (6) other options: azathioprine (AZA), mycophenolate mofetil (MMF), cyclosporine A (CsA) or rituximab (RTX) (online supplementary tables S2.1.1, S2.1.4, S2.1.6, S2.1.7, S2.2.11, S2.1.11, S2.1.12, S2.1.14, S2.1.15, S2.1.17, S2.2.1, S2.2.2, S2.2.4, S3.1.1, S3.1.3–S3.1.6, S3.2.1, S3.2.2, S12.2–S12.5, S12.8–S12.10).

Table 1 GLADEL–PANLAR recommendations for musculoskeletal and cutaneous manifestations in patients with systemic lupus erythematosus

Treatment recommendations	Quality of the evidence	Strength of recommendation
Musculoskeletal (MSK) manifestations		
In adult patients with SLE and MSK manifestations		
First line: Use SOC (GCs and AMs) alone over adding other IS.	Low	Weak
If disease remains active after SOC, add either MTX or LFN or belimumab or ABT over other IS.	Low to moderate	Weak
Cutaneous manifestations		
In adult patients with different manifestations of cutaneous lupus		
First line: Use SOC alone over adding other IS.	Low	Weak
If disease remains active after SOC, add MTX, AZA, MMF, CsA, CYC or belimumab over other IS.	Low to moderate	Weak

ABT, abatacept; AM, antimalarials; AZA, azathioprine; CsA, cyclosporine A; CYC, cyclophosphamide; GC, glucocorticoid; GLADEL, *Grupo Latino Americano de Estudio del Lupus*; IS, immunosuppressant; LFN, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; PANLAR, Pan-American League of Associations of Rheumatology; SLE, systemic lupus erythematosus; SOC, standard of care.

Benefits and harms

Although the panel judged that compared with SOC alone, adding MTX, LFN, belimumab or ABT is possibly associated with beneficial effects, a significant proportion of patients will achieve adequate symptom control with SOC and could be spared the adverse effects/excess costs associated to those other options.

Recommendation

The panel suggests SOC alone over adding other immunosuppressant (IS) in adult patients with SLE with MSK manifestations (weak recommendation based on low certainty of the evidence). It suggests also adding either MTX, LFN, belimumab or ABT to those failing to respond to SOC (weak recommendation based on low to moderate certainty of the evidence). Cost and availability may favour MTX (table 1).

Cutaneous manifestations

a. Which is the best treatment for adult patients with different manifestations of cutaneous lupus?

Interventions considered

(1) SOC; (2) SOC plus MTX; (3) SOC plus AZA; (4) SOC plus MMF; (5) SOC plus CsA; (6) SOC plus belimumab; (7) SOC plus ABT; (8) SOC plus acitretin; (9) SOC plus atacicept; (10) SOC plus cyclophosphamide (CYC) (online supplementary tables S4.1.1–S4.1.7, S4.2.1–S4.2.5, S4.3.1, S4.4.1, S4.4.2, S4.5.1–S4.5.13).

Benefits and harms

The panel judged that a significant proportion of patients will achieve adequate symptom control with SOC and could be spared the adverse effects/costs of the other therapies.

Recommendation

The panel suggests SOC alone over adding other IS in adult patients with SLE with cutaneous manifestations (weak recommendation based on low certainty of the evidence). It also suggests adding MTX, AZA, MMF, CsA, CYC or belimumab to patients failing to respond to SOC (weak recommendation based on low to moderate certainty of the evidence). Cost and availability may favour MTX and AZA (table 1).

Adult kidney manifestations

a. Which is the best induction treatment for adult patients with lupus nephritis?

Interventions considered

(1) GCs; (2) GCs plus high-dose CYC; (3) GCs plus low-dose CYC; (4) GCs plus MMF; (5) GCs plus RTX plus MMF; (6) GCs plus tacrolimus (TAC); (7) GCs plus AZA (online supplementary tables S1.1.1.2, S1.1.1.7, S1.1.1.8, S1.1.1.10, S1.1.2.2, S1.1.2.5, S1.1.2.7, S1.1.3.2, S1.1.4.1, S1.2.6).

Benefits and harms

Based on the identified evidence the panel concluded that compared with GCs alone, the addition of other IS (CYC, MMF or TAC) is associated with significant benefits, higher remission rates and lower progression rates to end-stage renal disease (ESRD). Head-to-head comparisons between MMF, TAC and high-dose CYC showed that MMF and TAC are associated with less adverse effects than high-dose CYC. Between low and high-dose CYC the balance favours the former because of better safety profile and comparable efficacy, although this conclusion is based on one trial that included predominantly Caucasians. RTX did not provide additional benefits when combined with MMF.

Recommendation

The panel recommends SOC (GCs and antimalarials (AM)) in addition to an IS (CYC in high or low doses, MMF or TAC) over GCs alone, for induction in patients with SLE-related kidney disease (strong recommendation based on moderate certainty of the evidence). Although more African-American descendants and Hispanic patients responded to MMF than CYC (25), limited access to MMF and TAC in several Latin American countries, due primarily to cost issues, makes CYC the best alternative for induction (high or low dose) in these regions (table 2).

b. Which is the best maintenance treatment for adult patients with lupus nephritis?

Interventions considered

Recommendations are applicable to patients showing partial or total remission after induction therapy aiming at sustaining renal remission, preventing relapses and achieving the best long-term outcome. The following interventions were considered: (1) AZA; (2) MMF; (3) CYC; (4) TAC; and (5) CsA (online supplementary tables S1.1.1.7, S1.1.2.1, S1.1.2.2, S1.2.1, S1.2.3, S1.2.4, S1.2.5, S1.2.6, S1.2.7).

Benefits and harms

The panel concluded that long-term IS agents during maintenance therapy prolong stable renal function, reduce proteinuria, extend renal survival and minimise the toxicity of GCs. AZA, CYC, MMF and CsA seem to be equivalent regarding efficacy but MMF and AZA have a better safety profile, particularly regarding gonadal toxicity and blood pressure control. We found very low certainty of the evidence for TAC as maintenance therapy, with studies mostly restricted to Asian populations.

Table 2 GLADEL–PANLAR recommendations for adult and childhood-onset lupus nephritis

Lupus nephritis		
Treatment recommendations	**Quality of the evidence**	**Strength of recommendation**
Induction therapy for adult patients with lupus-related nephritis		
Use SOC (GCs and AMs) plus another IS agent (CYC, MMF or TAC) over GCs alone.	Moderate	Strong
Maintenance therapy for adult patients with lupus-related nephritis		
Use MMF or AZA over CYC.	Low	Strong*
Induction therapy for childhood patient with lupus-related nephritis		
Use high-dose GCs (prednisone 1–2 mg/kg/day, maximum 60 mg/day) plus another IS agent (MMF or CYC) over high-dose GCs alone.	Low	Weak
Maintenance therapy for childhood patient with lupus-related nephritis		
Use MMF or AZA over CYC.	Low	Weak

*Strong recommendation supported on high certainty in less adverse events with MMF or AZA than with CYC.
AM, antimalarials; AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; GLADEL, *Grupo Latino Americano de Estudio del Lupus*; IS, immunosuppressant; MMF, mycophenolate mofetil; PANLAR, Pan-American League of Associations of Rheumatology; SOC, standard of care; TAC, tacrolimus.

Recommendation

The panel recommends AZA or MMF over CYC for maintenance in patients with SLE-related nephritis (strong recommendation based on low certainty of the evidence, since certainty in better efficacy of MMF or AZA over CYC is low but certainty of fewer adverse effects is high). Cost and availability issues may favour AZA (table 2).

Childhood-onset lupus nephritis

a. Which is the best induction treatment for childhood-onset lupus nephritis (cLN)?

Interventions considered

(1) MMF plus GCs; (2) CYC plus GCs; (3) GCs (online supplementary table S9.2.3).

Benefits and harms

The panel concluded that both MMF plus high-dose GCs (prednisone 1–2 mg/kg/day, maximum 60 mg/day) and CYC plus high-dose GCs are associated with significant benefits in comparison to GCs alone. No significant differences between these two alternatives were noted. The panel pointed that differential pharmacokinetic effects of MMF in cLN may exist, which could require dosing increase.[30] Risk of reduction of ovarian reserve and sperm abnormalities should be considered in patients with cLN treated with CYC.

Recommendation

The panel suggests high-dose GCs plus MMF or CYC over high-dose GCs alone in patients with cLN as induction therapy (weak recommendation based on low certainty of the evidence). Cost and availability may favour CYC despite the risk of gonadal toxicity (table 2).

b. Which is the best maintenance treatment for cLN?

Interventions considered

(1) SOC plus MMF; (2) SOC plus AZA (online supplementary table S9.2.3).

Benefits and harms

The panel concluded that MMF or AZA decreases the occurrence of ESRD without significant adverse events, as maintenance therapy for cLN. The panel pointed that differential pharmacokinetic effects of MMF in cLN may exist, which may require dosing increase.[30]

Recommendation

The panel suggests MMF or AZA over CYC for patients with cLN who responded, partially or completely, to induction therapy (weak recommendation based on low certainty of the evidence). Cost and availability may favour AZA (table 2).

Cardiac manifestations

a. Which is the best treatment for adult patients with lupus-related acute pericarditis?

Interventions considered

(1) SOC plus colchicine; (2) SOC plus non-steroidal anti-inflammatory drugs (NSAID); (3) SOC plus belimumab; (4) low to moderate dose of GCs for 4 weeks and slow tapering (online supplementary tables S6.2.1 and S6.3.1).

Benefits and harms

Based on the identified evidence the panel concluded that the use of SOC combined with colchicine is associated with significant benefits (decrease in pericarditis recurrence rate) compared with SOC alone. Belimumab probably made little or no difference in pericarditis-related symptom improvement.

Recommendation

The panel suggests SOC plus colchicine over SOC plus NSAIDs or belimumab for patients with acute SLE-related pericarditis (weak recommendation based on low certainty of the evidence) (table 3).

Pulmonary manifestations

a. Which is the best treatment for lupus-related diffuse alveolar haemorrhage (DAH)?

Table 3 GLADEL–PANLAR recommendations for cardiac and pulmonary manifestations

Treatment recommendations	Quality of the evidence	Strength of recommendation
Cardiac manifestations		
In adult patients with lupus-related acute pericarditis		
Use SOC plus colchicine over SOC plus NSAIDs or belimumab.	Low	Weak
Pulmonary manifestations		
In adult patient with lupus-related diffuse alveolar haemorrhage		
Use intravenous GCs plus CYC and/or intravenous Ig and/or TPE and/or RTX over GCs alone.	Very low	Strong*

*Strong recommendation supported on possible benefits in the context of a life-threatening situation.
CYC, cyclophosphamide; GC, glucocorticoid; GLADEL, *Grupo Latino Americano de Estudio del Lupus*; Ig, immunoglobulin; NSAID, non-steroidal anti-inflammatory drug; PANLAR, Pan-American League of Associations of Rheumatology; RTX, rituximab; SOC, standard of care; TPE, therapeutic plasma exchange.

Interventions considered

(1) High-dose GCs plus CYC; (2) high-dose GCs plus intravenous immunoglobulins (Ig); (3) high-dose GCs plus therapeutic plasma exchange (TPE); (4) high-dose GCs plus RTX (online supplementary tables S6.1.1 and S6.1.2).

Benefits and harms

In the absence of trustworthy evidence regarding the effects of the different interventions in this scenario and considering DAH's high mortality rate, the panel decided that intense and early approach is mandatory without prioritising one intervention over another.

Recommendation

The panel recommends that patients with SLE-related DAH be treated with intravenous GCs plus CYC and/or intravenous Ig and/or TPE and/or RTX over GCs alone (strong recommendation based on very low certainty of the evidence, since possible benefits exist in a life-threatening situation). Cost and availability may favour GC plus CYC (table 3).

Neuropsychiatric manifestations

a. Which is the best treatment for adult patients with lupus-related severe, acute neuropsychiatric manifestations?

Interventions considered

(1) High-dose GCs; (2) high-dose GCs plus CYC; and (3) high-dose GCs plus RTX (online supplementary tables S5.1.1, S5.1.2, S5.1.3, S5.1.6, S5.2.1, S5.2.3, S5.3.3, S5.4.1, S5.4.3, S5.5.1, S5.5.2, S5.6.1).

Benefits and harms

The panel concluded that both options (GCs plus CYC and GCs plus RTX) were associated with large benefits and moderate harms in comparison to GCs plus placebo in patients with acute neurological manifestations. No studies comparing these two options were identified. In terms of SLE and severe neurological manifestations, clinical trials with GCs plus CYC focused on both general neurologic manifestations, and on seizures, psychosis, myelitis, peripheral neuropathy, brain stem disease and optic neuritis, specifically. No data were found regarding other neuropsychiatric manifestations. The panel significantly weighted the fact that the certainty of the evidence was better for CYC than RTX and that RTX was only evaluated in refractory patients.

Recommendation

The panel suggests using GCs plus CYC over GCs alone or GCs plus RTX for the treatment of severe neurologic manifestations in patients with SLE (weak recommendation based on low certainty of the evidence). Cost and availability may favour CYC (table 4).

Haematological manifestations

a. Which are the best interventions for patients with severe acute lupus-related haemolytic anaemia (haemoglobin ≤8 g/dL)?

Interventions considered

(1) High-dose GCs; (2) GCs plus RTX (online supplementary tables S7.1.12 and S7.1.13).

Table 4 GLADEL–PANLAR recommendations for neuropsychiatric and haematological manifestations

Treatment recommendations	Quality of the evidence	Strength of recommendation
Neuropsychiatric manifestations		
In adult patients with lupus-related severe, acute neuropsychiatric manifestations		
Use GCs plus CYC over GCs alone or GCs plus RTX.	Low	Weak
Haematological manifestations		
In patients with severe acute lupus-related haemolytic anaemia (haemoglobin ≤8 g/dL)		
Use high-dose GCs.	Low	Weak
If life-threatening or haemolytic anaemia remains active use RTX. Cost and availability may prompt the use of IS over RTX.	Low	Weak
In patients with severe lupus-related thrombocytopenia (platelet count ≤30 x10^9/L)		
Use high-dose GCs.	Moderate	Weak
If first line failure, or life-threatening bleeding, urgent surgery or patients with current and ongoing infections: Use intravenous Ig with/without GCs or RTX plus GCs. Cost and availability may prompt the use of IS over RTX.	Moderate	Strong

CYC, cyclophosphamide; GC, glucocorticoid; GLADEL, *Grupo Latino Americano de Estudio del Lupus*; Ig, immunoglobulin; IS, immunosuppressant; PANLAR, Pan-American League of Associations of Rheumatology; RTX, rituximab.

Benefits and harms

The panel concluded that compared with GCs as the first-line therapy, the addition of RTX provided moderate beneficial effects (reducing the risk of flare) and moderate harms (increasing the risk of infections). However, the panel significantly weighted the risks associated with RTX as well as availability and cost issues.

Recommendation

The panel suggests using high-dose GCs for patients with severe haemolytic anaemia (weak recommendation based on low certainty of the evidence).

It also suggests RTX for patients with life-threatening haemolytic anaemia and/or for those in whom high-dose GC treatment fails (weak recommendation based on low certainty of the evidence). Cost and availability, however, may prompt the use of IS instead of RTX although no data support this assertion (table 4).

a. Which are the best interventions for patients with severe lupus-related thrombocytopenia (platelet count ≤ 30 x10^9/L)?

Interventions considered

(1) High-dose GCs; (2) high-dose GCs plus RTX; (3) high-dose GCs plus intravenous Ig (online supplementary tables S7.1.12, S7.1.13, S7.1.15).

Benefits and harms

The panel concluded that compared with GCs as the first-line therapy, RTX and intravenous Ig provided moderate beneficial effects (increasing the platelet count). The harmful effects were judged as moderate for RTX (increase in infections) and small for intravenous Ig (infusion reactions).

The panel significantly weighted the risks associated with RTX as well as availability and cost issues. In life-threatening situations, the panel significantly weighted intravenous Ig's and RTX's beneficial effect on platelet count.

Recommendations

The panel suggests using high-dose GCs in patients with lupus with severe lupus thrombocytopenia (weak recommendation based on moderate certainty of the evidence).

It also recommends intravenous Ig with/without GCs or RTX plus GCs for patients who are refractory to high-dose GCs, those with life-threatening bleeding, those requiring urgent surgery and those with infections (strong recommendation based on moderate certainty of the evidence). Cost and availability, however, may prompt the use of IS instead of RTX although there are no data to support this assertion (table 4).

Antiphospholipid syndrome

a. Which is the best treatment for adult patients with SLE with antiphospholipid syndrome (APS) and venous thromboembolic disease (VTD)?

Interventions considered

(1) Extended anticoagulation (AC) with vitamin K antagonist (compared with not-extended AC); (2) high-intensity AC (international normalised ratio (INR) 3–4.5) compared with moderate-intensity AC (INR 2–3) (online supplementary tables S10.2.1 and S10.2.2).

Benefits and harms

The panel judged the effect of extended AC as a large benefit, reducing VTD with increase in bleeding risk as a moderate harm. For the comparisons of different AC intensities, the panel decided to use the evidence from observational studies because it judged that it probably better reflects reality given that the randomised controlled trials (RCT) are severely flawed (indirectness of intervention as most patients did not reach the INR >3 goal). They judged the reduction in VTD as a large benefit and the bleeding increase as a large harm. Hence, the panel considered that the balance could favour the intervention only when the risk of VTD recurrence is particularly high.

Recommendation

The panel recommends extended AC with vitamin K antagonist therapy for patients with APS with VTD (strong recommendation based on moderate certainty of evidence).

The panel recommends standard (INR 2.0–3.0) over high-intensity (INR 3.0–4.0) AC for patients with APS with VTD (strong recommendation based on very low certainty of the evidence, since certainty of the effect on VTD recurrence is very low but certainty in bleeding risk is high (significant increase in major bleeding with INR 3.0–4.0)).

b. Which is the best treatment for adult patients with SLE with APS and stroke?

Interventions considered

Extended antithrombotic therapy with: (1) vitamin K antagonist; (2) low-dose aspirin (LDA: 81–100 mg/day); (3) vitamin K antagonist plus LDA; (4) high-intensity AC (INR 3–4.5) (online supplementary tables S10.3.1 and S10.3.2).

Benefits and harms

The panel decided to use the body of evidence provided by observational studies because it probably better reflects reality as the RCTs are severely flawed (indirectness of population as most patients were inadequately diagnosed with APS). The panel judged the observed reduction in arterial thrombosis with high-intensity AC as a large benefit, and the bleeding increase as a large harm. Also, it was noted that the observed basal risk (risk with LDA) of thromboembolic recurrence in patients with APS and arterial events was particularly high, compared with the risk of recurrence in patients with VTD.

Recommendation

The panel suggests extended high-intensity (INR 3.0–4.0) over standard-intensity AC (INR 2.0–3.0) or LDA alone for patients with SLE with APS and stroke (weak recommendation based on very low certainty of the evidence).

c. Which is the best treatment for pregnant SLE women with antiphospholipid antibodies and recurrent pregnancy loss?

Interventions considered

(1) HCQ plus LDA; (2) HCQ plus LDA plus heparin; (3) HCQ plus intravenous Ig (online supplementary tables S10.5.1, S10.5.2, S10.5.3, S10.5.4, S10.5.5, S10.5.6, S10.5.7, S10.5.8).

Benefits and harms

The panel judged the observed reduction in pregnancy loss with the addition of heparin to LDA as a large benefit. This intervention was not associated with significant harms. The addition of GCs or intravenous Ig to heparin plus LDA was associated with large harms (significant increase in premature delivery) without relevant benefits. Regarding heparin administration, the panel considered the reduction in pregnancy loss with low molecular weight heparin (LMWH) in comparison with unfractionated heparin (UFH) as a large benefit without significant adverse effects. No additional benefits were observed with LMWH-enoxaparin 80 mg compared with 40 mg.

Recommendation

The panel recommends HCQ plus LMWH plus LDA over HCQ plus LDA or adding GCs or intravenous Ig for pregnant patients with SLE with antiphospholipid antibodies and recurrent pregnancy loss (strong recommendation based on moderate certainty of the evidence (LMWH plus LDA vs other alternatives) and very low certainty of the evidence (GCs and intravenous Ig vs other alternatives), since high certainty of harms related to GCs (increased premature delivery) and intravenous Ig (costs increase, burden related to drug administration) exists).

It also suggests LMWH at a dose of 40 mg/day over UFH or higher doses of LMWH (weak recommendation based on low certainty of the evidence) (table 5).

DISCUSSION

Treatment of SLE in Latin America remains a challenge despite several guidelines published on the management of this disease.[16–21] The distinct epidemiology, healthcare resources, socioeconomic issues and priorities were considered to develop these guidelines.

Although these guidelines consider region limitations, the inclusion of alternative approaches for tailoring treatment did not exclude the task of providing physicians with the state-of-the-art findings in the field. This was a major advantage of the present work since highlighting these advances provides valuable basis for future requirement of government authorisation of new drugs in these countries.

Of note, problems faced by Latin American countries are shared by several developing nations. Therefore, it is expected that these guidelines will also be very useful for them. Furthermore, due to ever increasing globalisation and the increase

Table 5 GLADEL–PANLAR recommendations for adult patients with SLE with antiphospholipid antibodies or antiphospholipid syndrome

Antiphospholipid syndrome		
Treatment recommendations	**Quality of the evidence**	**Strength of recommendation**
In adult patients with lupus with APS and venous thromboembolic disease		
Use extended over time-limited anticoagulation.	Moderate	Strong
Use standard-intensity anticoagulation (INR 2.0–3.0) over high-intensity anticoagulation (INR 3.0–4.0).	Very low	Strong*
In adult patients with SLE with APS and stroke		
Use high-intensity anticoagulation (INR 3.0–4.0) over standard-intensity anticoagulation (INR 2.0– 3.0) or LDA.	Very low	Weak
In pregnant lupus women with obstetric APS and recurrent pregnancy losses		
Use HCQ plus LMWH plus LDA over HCQ plus LDA, or adding GCs or intravenous Ig.	Moderate	Strong

*Strong recommendation supported on high certainty in significant bleeding risk increase with high-intensity anticoagulation.
APS, antiphospholipid syndrome; GC, glucocorticoid; GLADEL, *Grupo Latino Americano del Estudio de Lupus*; HCQ, hydroxychloroquine; Ig, immunoglobulin; INR, international normalised ratio; LDA, low-dose aspirin; LMWH, low molecular weight heparin; PANLAR, Pan-American League of Associations of Rheumatology; SLE, systemic lupus erythematosus.

of migratory movements of people from countries with more susceptible SLE groups in terms of frequency and disease severity both in terms of race/ethnicity (Mestizos, Asians, Africans) and low SES to countries with better life opportunities, we consider that these guidelines may be used by physicians anywhere in the world, even in developed countries, where such individuals may migrate to and seek care for their lupus.

We acknowledge as a limitation that certainty of the evidence was not as high as desirable for most recommendations and probably biased by few randomised clinical trials. Although regional information was published on several topics[1 4 10 11 23 24 31–49] we recognise that these guidelines should be updated as research-based changes in our understanding of SLE emerge. Regardless, the publication of these guidelines must be followed by health system engagement and implementation by specialists, major steps towards improvement of lupus treatment in Latin America and low/middle-income countries.

Author affiliations
[1]Departamento de Medicina Interna, Grupo Oroño-Centro Regional de Enfermedades Autoinmunes y Reumáticas (GO-CREAR), Rosario, Argentina
[2]Rheumatology Division, Faculdade de Medicina, Hospital das Clinicas HCFMUSP, Universidade de São Paulo, São Paulo, Brazil
[3]Sección de Reumatología, Servicio de Clínica Médica, Instituto Universitario, Escuela de Medicina, and Fundación Dr Pedro M Catoggio para el Progreso de la Reumatología, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
[4]Centro de Investigación Clínica de Morelia, SC, Morelia, México
[5]Servicio de Clínica Médica del Hospital Alemán de Buenos Aires, Hospital Alemán de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina
[6]Grupo de Inmunología Celular e Inmunogenética, Universidad de Antioquia, Hospital Universitario, Fundación San Vicente, Medellín, Colombia
[7]Centro de Biología Celular y Biomedicina, Facultad de Medicina y Ciencia. Universidad San Sebastián, Santiago, Chile
[8]Departamento de Reumatología, Hospital de Clínicas, Facultad de Ciencias Médicas, Universidad Nacional de Asunción, Asunción, Paraguay
[9]Hospital Angeles del Pedregal, Ciudad de México, México
[10]Servicio de Reumatología, HIGA General San Martín, La Plata, Argentina
[11]Servicio de Reumatología, Centro Médico ABC, Ciudad de México, México
[12]Servicio de Reumatología Infantil, Hospital de Niños Dr Ricardo Gutiérrez, Buenos Aires, Argentina
[13]Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paul, Brazil
[14]Discipline of Rheumatology, University of the State of Rio de Janeiro, Rio de Janeiro, Brasil
[15]Facultad de Medicina., Universidad Nacional Mayor de San Marcos. Servicio de Reumatología. Clínica San Felipe, J. María., Lima, Perú.
[16]Servicio de Reumatología, Policlínica Méndez Gimón, Caracas, Venezuela
[17]Unidad de Enfermedades Reumáticas y Autoinmunes (UNERA), Corporación Médica Monte Sinaí., Cuenca, Ecuador
[18]Universidad Nacional de Colombia, Bogotá, Colombia
[19]Centro Integral de Reumatología, Reumalab, Medellín, Colombia
[20]Sección de Reumatología, Hospital del Salvador. Universidad de Chile. Unidad de Reumatología. Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo., Santiago, Chile
[21]Pediatric Department, Faculdade de Medicina, Children's Institute, Hospital das Clinicas HCFMUSP, Universidade de São Paulo, São Paulo, Brazil
[22]Clínica Reumatológica, Universidad de la República, and Unidad Docente Asistencial, Hospital Pasteur, Instituto Nacional de Reumatología., Montevideo, Uruguay
[23]Servicio de Reumatología, Hospital Clinic, Barcelona, Spain
[24]Servicio de Reumatología, Hospital Provincial de Rosario, Rosario, Argentina
[25]Servicio de Reumatología, Hospital Italiano de Córdoba, Córdoba, Argentina
[26]Division of Rheumatology, Department of Medicine, Emory School of Medicine, Atlanta, Georgia, USA
[27]Servicio de Reumatología, Hospital Privado Universitario de Córdoba, Córdoba, Argentina
[28]Servicio de Reumatología, Hospital General Guillermo Almenara Irigoyen, EsSalud., Lima, Perú
[29]Universidad Científica del Sur, Lima, Perú
[30]Serviço de Reumatologia do Hospital das Clínicas da Universidade Federal de Pernambuco (HC-UFPE), Recife, Brazil
[31]Unidad de Reumatología, Departamento de Medicina, Universidad de Oriente, Complejo Hospitalario Universitario Ruiz y Páez, Ciudad Bolívar, Venezuela
[32]Serviço de Reumatologia, Departamento de Clinica Medica, Faculdade de Medicina, Hospital das Clínicas, Universidade Federal de Goiás, Goiânia, Brazil
[33]Departamento de Pediatría, Facultad de Medicina, Universidad de Antioquia, Hospital Pablo Tobón Uribe, Medellín, Colombia
[34]Servicio de Reumatología, Hospital General de Medellín 'Luz Castro de Gutierrez' ESE, ARTMEDICA, Medellín, Colombia
[35]Departamento de Inmunología y Reumatología, Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Ciudad de México, Mexico
[36]Unidad de Enfermedades Autoinmunes Sistémicas, Facultad de Medicina, Clínica Médica 'C', Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay
[37]Unidad de Reumatología y Enfermedades Autoinmunes Sistémicas, HIGA Dr Oscar Alende, Mar del Plata, Argentina
[38]Servicio de Reumatología, Enfermedades Reumatológicas e Investigación Clínica (ERIC), Hospital Docente Padre Billini, Santo Domingo, Dominican Republic
[39]Departamento de Clínica Médica, Disciplina de Reumatologia, Faculdade de Ciências Medicas da UNICAMP, Universidade Estadual de Campinas, Campinas, Brazil
[40]Servicio de Reumatología, Departamento de Especialidades Médicas, Hospital Nacional Edgardo Rebagliati Martins, EsSalud., Lima, Perú
[41]Servicio de Reumatología, CEIBAC, SC, Guadalajara, México
[42]Servicio de Inmunología, Instituto de Investigaciones Médicas "Alfredo "Lanari", Ciudad Autónoma de Buenos Aires, Argentina
[43]Servicio de Reumatología, Hospital Escuela "Eva Perón", Granadero Baigorria, Argentina
[44]Departamento de Inmunología, Instituto Nacional de Cardiología Ignacio Chávez, Ciudad de México, Mexico
[45]Departamento de Reumatología, Instituto Nacional de Cardiología "Ignacio Chávez", Ciudad de México, México
[46]Unidad de Reumatología, Cátedra de Clínica Médica I, Hospital Córdoba. Cátedra de Semiología, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba., Córdoba, Argentina
[47]Rheumatology Division, Department of Internal Medicine, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
[48]Departamento de Inmunología Clínica y Reumatología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[49]Departamento de Reumatología, Consultorio de Especialidades del Instituto Salvadoreño de la Seguridad Social, San Salvador, El Salvador
[50]Departamento de Inmunología y Reumatología, Hospital General de Occidente., Zapopan, Jalisco, México.
[51]Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Ciudad de México, Mexico
[52]Departamento de Reumatología, Hospital de Especialidades CMN SXXI, IMSS, Ciudad de México, Mexico
[53]Grupo de Trabajo en Enfermedades Autoinmunes Sistémicas, Servicio de Clínica Médica, Facultad de Medicina, Universidad de la Republica, Hospital Pasteur, Administración de Servicios de Salud del Estado, Montevideo, Uruguay
[54]Servicio Nacional de Reumatología, Centro de Investigaciones Médico Quirúrgicas (CIMEQ)., La Habana, Cuba

[55]Servicio de Reumatología, Instituto de Rehabilitación Psicofísica (IREP), Ciudad Autónoma de Buenos Aires, Argentina
[56]Division of Clinical Immunology and Rheumatology, Department of Medicine, School of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama, USA
[57]Department of Medicine, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru

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