



Évaluer la dose optimale de glucocorticoïdes pour traiter la néphrite lupique : une collaboration entre Bordeaux et Bilbao

Cécile Saint-Pastou Terrier

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**Evaluer la dose optimale de glucocorticoïdes pour
traiter la néphrite lupique :
Une collaboration entre Bordeaux et Bilbao.**

Assess the optimal dose of glucocorticoids to treat lupus nephritis: collaboration between Bordeaux and Bilbao.

Directrice de thèse :

Madame le Professeur Estibaliz LAZARO,

Rapporteur de thèse :

Monsieur le Docteur Pierre DUFFAU,

Membres du Jury :

Monsieur le Professeur Patrick BLANCO,

Président

Monsieur le Professeur Lionel COUZI,

Juge

Monsieur le Professeur Christophe RICHEZ,

Juge

Monsieur le Professeur Guillermo RUIZ-IRASTORZA,

Juge

Madame le Docteur Amaia UGARTE NUÑEZ,

Invitée

“Guérir parfois, soulager souvent, écouter toujours.”

Louis Pasteur

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AU PRESIDENT DU JURY

Monsieur le Professeur Patrick Blanco,

*Professeur des Universités,
Praticien Hospitalier,
Chef de service d'immunologie et d'immunogénétique,
Groupe Hospitalier Pellegrin, Centre Hospitalier Universitaire de Bordeaux.
Coordinateur du groupe de Recherche « Mécanismes immunitaires de l'auto-immunité » au
centre de recherches Immunology from Concept and Experiments to Translation
(ImmunoConcept) CNRS UMR 5164, Université de Bordeaux.*

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Madame le Professeur Estibaliz LAZARO,

*Professeur des Universités,
Praticien Hospitalier,
Service de médecine interne et maladies infectieuses,
Hôpital Haut Lévêque – Groupe Hospitalier Sud, Centre Hospitalier Universitaire de Bordeaux.
Chercheur centre de recherches ImmunoConcept CNRS UMR 5164, Université de Bordeaux.*

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*Maître de conférences des universités,
Praticien Hospitalier,
Service de médecine interne et maladies infectieuses
Hôpital Saint-André, Centre Hospitalier Universitaire de Bordeaux,
Chercheur centre de recherches ImmunoConcept CNRS UMR 5164, Université de Bordeaux*

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*Professeur des Universités,
Praticien Hospitalier,
Service de Néphrologie – Transplantation – Dialyse - Aphérèses
Groupe Hospitalier Pellegrin, Centre Hospitalier Universitaire de Bordeaux.
Chercheur centre de recherches ImmunoConcept CNRS UMR 5164, Université de Bordeaux.*

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*Profesor Titular en la U.D. Facultad de Medicina y Odontología en Cruces Dpto, Universidad del País Vasco, Euskal Herriko Unibertsitatea Leio, España.
Doctor en Medicina,
Jefe de sección de Enfermedades Autoinmunes, Hospital Universitario Cruces, Barakaldo, País Vasco, España.
Coordinador del Grupo de investigación "Enfermedades Autoinmunes, Inflamatorias e Infecciosas" al Instituto de Investigación Sanitaria de la OSI Ezkerraldea Enkarterri Cruces (Biocruces), Barakaldo, País Vasco, España.*

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*Professeur des Universités,
Praticien Hospitalier,
Service de médecine interne et maladies infectieuses
Hôpital Saint-André, Centre Hospitalier Universitaire de Bordeaux.
Chercheur centre de recherches ImmunoConcept CNRS UMR 5164, Université de Bordeaux.*

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*Doctor en Medicina, Enfermedades Autoinmunes, Hospital Universitario Cruces, Barakaldo, País Vasco, España.
Investigador en el grupo "Enfermedades Autoinmunes, Inflamatorias e Infecciosas" al Instituto de Investigación Sanitaria de la OSI Ezkerraldea Enkarterri Cruces (Biocruces), Barakaldo, País Vasco, España.*

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Glossary

- **ACR:** American College of Rheumatology
- **AMM:** autorisation de mise sur le marché (French marketing authorization for a new drug)
- **aPL** antiphospholipid
- **BC:** Bordeaux cohort
- **BMD:** bone mass density
- **C-GR:** cytosolic glucocorticoid receptor
- **CC:** Cruces-protocol cohort
- **CCL2:** chemokine ligand 2
- **CCL7:** Chemokine (C-C motif) ligand (MCP3).
- **CCL8:** Chemokine (C-C motif) ligand 8
- **COX :** Cyclo-oxygenase
- **CR:** complete remission
- **CVEs:** cardiovascular events
- **CXCL8:** CXC-chemokine ligand 8
- **CYC:** cyclophosphamide
- **DC:** dendritic cell
- **ERA-EDTA:** European renal association -European dialysis and transplant association
- **ESRD:** End-stage renal disease
- **EULAR:** European League Against Rheumatism
- **GCs:** Glucocorticoids
- **GM-CSF:** Granulocyte-macrophage colony-stimulating factor
- **GRE:** Glucocorticoid Response Element
- **GRs:** Glucocorticoid receptors
- **HAS :** Haute autorité de santé
- **HC:** Historic cohort
- **HCQ:** Hydroxychloroquine
- **IFN:** interferon
- **IL-1RA:** Interleukin-1 Receptor Antagonist
- **IL:** Interleukin
- **IV:** intravenous
- **KDIGO:** Kidney Disease: Improving Global Outcomes
- **LN:** lupus nephritis
- **MCP1:** Monocyte chemoattractant protein 1
- **MCP2:** monocyte chemoattractant protein 2
- **MCP3:** monocyte-chemotactic protein 3
- **mGCR:** membrane-bound glucocorticoid receptor
- **MHC:** Major histocompatibility complex
- **MMF:** mycophenolate mofetil
- **MP:** Methylprednisolone
- **NF- κ B:** nuclear factor-kinase B
- **NIH:** National Institutes of Health
- **NK cell:** Natural killer cell
- **OP:** osteoporosis
- **PDC:** plasmacytoid dendritic cells
- **PNDS:** Protocol national de diagnostic et de soins
- **SLE:** Systemic lupus erythematosus
- **SNPs:** Single nucleotide polymorphisms
- **sVCAM-1:** soluble vascular cellular adhesion molecule-1
- **T-cell:** T lymphocyte

- **TLR:** Toll like receptor
- **TNF:** Tumor necrosis factor
- **vs:** versus
- **vWf:** von Willebrand factor

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Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with a wide range of clinical manifestations due to immunological alterations. General fatigue, skin rash, fever, and arthritis are common symptoms in SLE, but visceral organ involvement such as heart, lung, nervous system and kidney can result in severe disease status. Among these organ complications, lupus nephritis most strikingly influences the course of SLE. Renal involvement may be the first manifestation of SLE, but most commonly, it occurs within a year of diagnosis and almost always within 5 years, even if it can occur at any time throughout the course of the disease (1). It can affect over half of all patients with SLE depending in particular on ethnic origins (2,3). LN occurred in 38.3% of SLE patients, frequently as the initial presentation, in a recent large multi-ethnic inception cohort (4). A study from northwest England yielded incidence and prevalence of 0.40 per 100,000 population per year and 4.4 per 100,000 population, respectively (5). Ten to thirty percent of patients with lupus nephritis (LN) class III and above (according to the classification of glomerulonephritis in SLE revisited (6)) progress to end-stage renal disease (ESRD) resulting in kidney transplantation or haemodialysis (7–9). Renal damage is a severe SLE manifestation, carries excessive mortality and morbidity and is considered as a predictor of mortality in SLE patients, irrespectively of ethnicity (4,9–11).

In the first few years of illness, the major causes of mortality are severe infections due to immunosuppression or deaths from complications of active disease such as LN, while causes of late death include damage from chronic SLE (ESRD), treatment complications, and cardiovascular disease that appeared to be associated with long term steroid usage (8,12).

The therapeutic management of SLE is still a great debate and there is not a common approach for treating SLE. For decades glucocorticoids (GCs) have been the first and the most frequently therapy choice used as immune suppressive agents in SLE via oral route or with pulse therapy in order to abrogate acute deterioration of renal function in lupus nephritis patients. GCs still remain the most important therapy in SLE in daily routine (13,14).

The response to GCs differs widely from one patient to another and long-term therapy is usually associated with side effects. Controversy remains over the optimal use of GCs in LN in terms of their impact on disease activity, clinical outcomes and associated toxicity, partly due to the lack of enough evidence based medicine and randomised trial evidence. Still now, clinicians and physicians are unable to predict the exact and ideal dose and term of therapy for patients suffering from various symptoms and degree of disease activity of SLE. Even if GCs have undeniable benefits, the current trend is to use the lowest dose to control the lupus disease and taper it at soon as possible (13,15).

I. The optimal dose of Glucocorticoids to treat lupus nephritis

Firstly, we will focus on the corticosteroid sensitivity of SLE and the role of GCs in managing the disease. Then we will have a look at the present recommendations for the treatment of LN. Next, we will consider the side effects of GCs therapy. Finally we will explore recent data showing positive findings towards treating LN with a steroid-sparing regimen.

1. The role of steroids in managing systemic lupus erythematosus

1.1 Mechanisms of action of GCs: anti-inflammatory and immunosuppressive actions

GCs (which includes Cortisone, Dexamethasone, Prednisolone, Prednisone, Methylprednisolone) are essential hormones for homeostasis and have anti-inflammatory and immunosuppressive effects, involving GCs-responsive cascades, transcription factors, and cytokines (13).

Synthetic GCs diffuse rapidly into tissues where they are metabolised, particularly in the liver by 11 β -hydroxysteroid dehydrogenase enzymes to active 11- β -hydroxyl compounds (16). The GCs hormones are highly lipophilic molecules that easily pass through cellular membranes, reaching the cytosol and interacting with intracellular structures (13,17,18).

1.1.1 Glucocorticoids effects on immune-cell trafficking

These steroid hormones exert their anti-inflammatory and immunosuppressive effects by reducing the expression of cytokines and inhibiting the expression of many cell-adhesion molecules that are involved in cell trafficking. Glucocorticoids also inhibit the production and secretion of chemokines, such as CC-chemokine ligand 2 (CCL2; also known as MCP1) and CXC-chemokine ligand 8 (CXCL8; also known as IL-8) by eosinophils. Finally, GCs downregulate T-cell expression of CCL8 (also known as MCP2) and CCL7 (also known as MCP3), which are chemotactic for many cell types including monocytes, DCs, and natural killer (NK) cells. Thereby they inhibit T cell activation, leukocyte traffic and access to inflammation site by interfering with leukocyte, fibroblast and endothelial cell functions (17,19–27).

1.1.2 Glucocorticoids effects on immune-cell functions

GCs have strong anti-inflammatory and immunosuppressive effects on both acquired and innate immune functions. Almost all primary and secondary immune cells are targets for their effects. In general, GCs suppress maturation, differentiation and proliferation of all immune cells, including DCs and macrophages. GCs also reduce the capacity of DCs to promote allostimulatory responses and efficient activation of naive T cells, possibly owing to downregulation of expression of MHC class II (Major histocompatibility complex) and co-stimulatory molecules. In addition to inhibiting B and T cell responses and effector functions of monocytes and neutrophils, GCs reduce the overall number of circulating T-cells and diminish the number of circulating monocytes and macrophages by decreasing their myelopoiesis and their release from the bone marrow. Besides, they reduce the expression of Fc receptors. GCs act on immune cells both directly and indirectly to suppress the induction of pro-inflammatory responses by reducing the production of pro-inflammatory cytokines such as Interleukin (IL)-2, IL-6, IL-1 β , Tumor necrosis factor (TNF)- α and block prostaglandin synthesis at an early step in the pathway, prior to arachidonic acid synthesis via the inhibition of COX-2 (cyclooxygenase 2) activity, while promoting the production of anti-inflammatory cytokines, such as IL-10, by macrophages and DCs. In addition GCs also promote apoptosis of macrophages, DCs and T cells, leading to inhibition of immune response and affect granulocyte function by increasing the number of circulating neutrophils and reducing the amount of eosinophils and basophils (17,19,21,22).

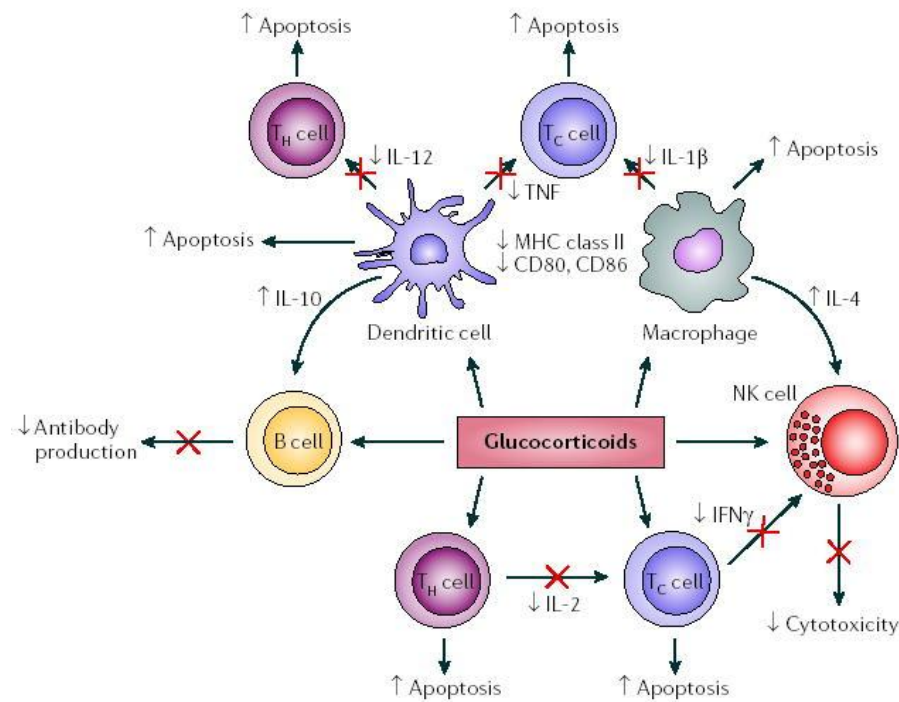


Figure 1: Mechanisms of action of Glucocorticoids: anti-inflammatory and immunosuppressive actions adapted from EM Sternberg et al (21).

1.2 Glucocorticoid Receptors (GRs)

The response to GCs depends on the expression of two glucocorticoid receptors (GRs), GR α and GR β . The biological mechanisms, the anti-inflammatory and immunosuppressive effects of GCs are regulated through activation of these GRs. The GR α is the predominant isoform which binds steroids and regulate transactivation of target genes whereas the GR β , a C-terminal modified form of the GR α , is not able to bind GCs. These effects are mediated by two different mechanisms of action: cytosolic glucocorticoid receptor (cGCR)-mediated classical genomic and rapid non-genomic effects, membrane-bound glucocorticoid receptor (mGCR)-mediated non-genomic effects and non-specific non-genomic effects (19).

Despite the strong biological action of GCs, the efficiency of GCs fluctuates among SLE patients. The efficiency of GCs not only relays on the doses of GCs but strongly depends on the density and affinity of the glucocorticoid receptors (GRs). Due to the high number of GR isoforms, sensitivity to GCs and therefore their efficiency vary among individuals and even within different tissues from the same individual (13,16). Many studies also showed that the GR α expression correlated with disease activity and the GR gene SNPs (Single nucleotide polymorphisms) (13,28–30).

1.3 Mechanisms of action of GCs: the genomic and non-genomic pathways

The anti-inflammatory and immunosuppressive actions of GCs are exerted by two different mechanisms: the genomic and non-genomic pathways.

1.3.1 Genomic pathway

In the genomic pathway, GCs modulate the expression of proteins via their interaction with the cGR, which is a member of the steroid hormone receptor family, a super-family of ligand-inducible transcription factors.

After reaching the cytosol, GCs are available to bind with high affinity to the cytosolic GR that becomes activated. Upon contact with GCs, GRs undergo a conformational change that triggers their translocation to the nucleus where the GCs-GR complex binds to specific DNA binding sites, the

Glucocorticoid Response Element (GRE). GR can therefore alter target genes, which can modify the target cells and organs (13,17,31,32).

The interaction between the GCs-GR complex and GRE determines modulation of gene expression either positively, called transactivation or negatively, called transrepression. Transrepression induced by the GCs-GR complex with the negative GRE binding sites inhibits many pro-inflammatory molecules and it became one of the most important explanations for the immunosuppressive and anti-inflammatory effects of GCs. Activated GR can bind to key transcription factors, like nuclear factor- κ B (NF- κ B) and repress the activity of many important pro-inflammatory genes and of a growing list of immune-regulating transcription factors (13,16,17,33–37).

In contrast, transactivation is responsible for transcription of enzymes linked to gluconeogenesis and other adverse reactions. Therefore, transactivation appears as the main mechanism involved in most adverse effects of GCs (16,17,19). Even if the processes by which the GCs activate then modulate the protein expression take less than an hour, the genomic pathway is a very slow process. In fact the overall immunosuppressive and anti-inflammatory effects via the genomic pathway manifest late and will take hours or days before they are efficient (16,17,38,39).

1.3.2 Non-genomic pathway

On the other side, there is a faster mechanism, known as the non-genomic pathway, which provides part of the rapid immunosuppressive and anti-inflammatory effects. It is well known that high and very high systemic methylprednisolone doses may quickly improve many processes such as systemic autoimmune disease flares (17,40,41).

The non-genomic pathway offers three mechanisms: First, GCs can interact with the cGR in a GR-dependent but non genomic pathway (transcriptional-independent mechanism) where the GR complex, after binding to GCs, is able to interact with intracellular proteins, leading to a rapid inhibition of inflammatory mediators such as arachidonic acid. Secondly, GCs may produce their effects by interacting with biological membranes, particularly cellular and mitochondrial membranes and therefore, GCs can reduce ATP that is essential for immune cells to maintain their functions. Thirdly, GCs may interact with a membrane-bound GR (17,40,41).

The cooperation between these transcriptional factors and the monomeric GRs can coordinate the transcriptional activation of genes involved in inflammatory diseases. There are several transcriptional factors, which interact with GRs and contribute to the transrepression such as c-Jun, c-Fos, activator protein 1, NF- κ B. At cellular level, the primary anti-inflammatory mechanism of GCs is thought to be NF- κ B inhibition. A wide range of anti-inflammatory cytokines are enhanced by GCs, such as Interleukin-1 Receptor Antagonist (IL-1RA), IL-10, secretory leukocyte inhibitory protein and neutral endopeptidase. Pro-inflammatory cytokines (such as IL-1, IL-2, IL-3, IL-6, IL-8, IL-11, IL-12, TNF- α , INF- γ , and GM-CSF) can suppress or inhibit GRs function and may develop the glucocorticoid resistance (13,42,43).

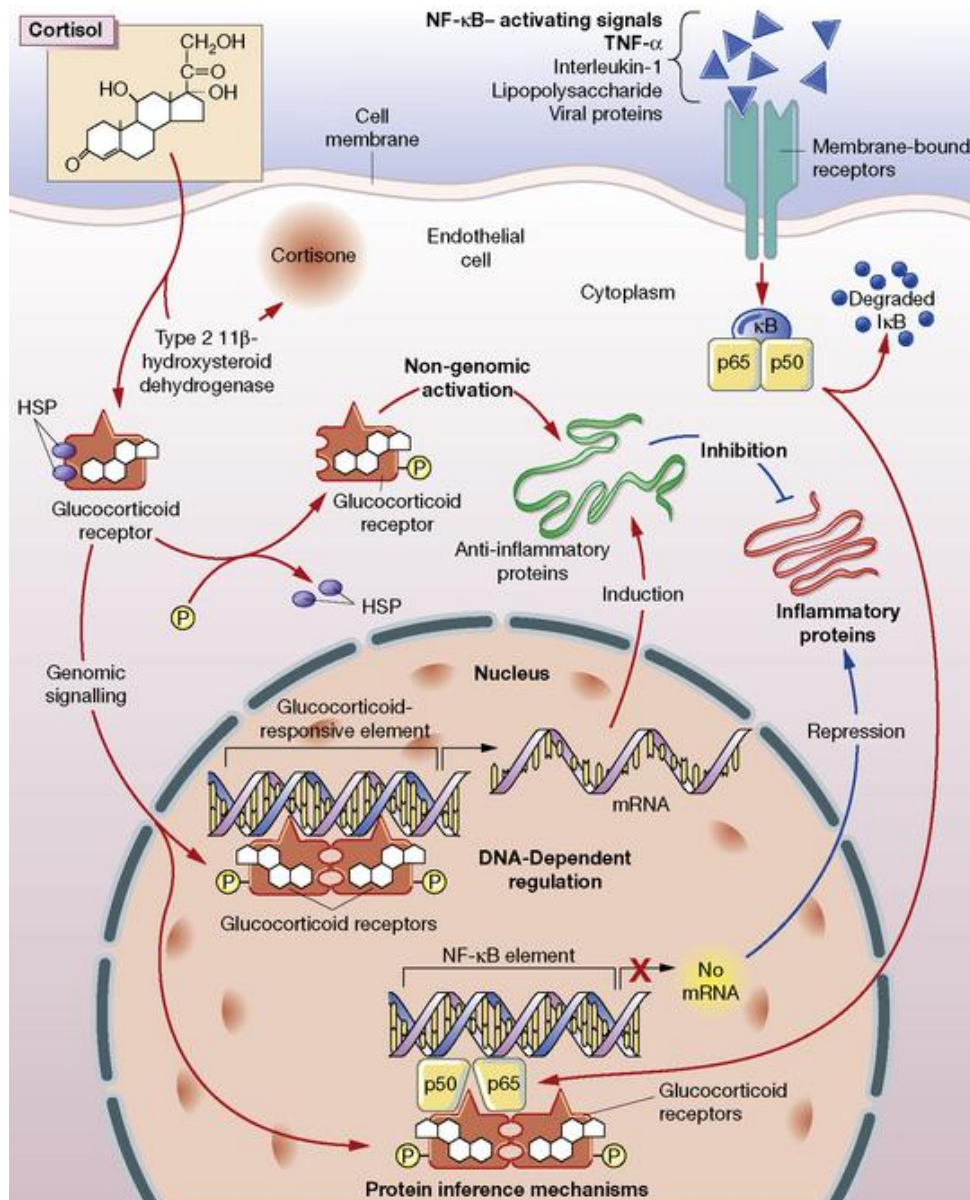


Figure 2: Mechanisms of action of GCs: Genomic and Non-Genomic pathways adapted from Rhen T et al (18).

1.3.3 Dose related GCs effect

The capacity to recruit both genomic and non-genomic pathways is different for the different steroids compounds. Besides, genomic effects are related with the degree of cytosolic receptor saturation even though there is no such exact linear relationship between them. At doses up to 30 mg/day of prednisone or equivalent, the cGR is saturated up to 50%. GR saturation reaches 100% above that dose. In other words, between 30 and 100 mg/day of prednisone-equivalent, the genomic way is fully operating. In contrast, the non-genomic pathway is operating, at clinically relevant levels, at doses >100mg/ day of prednisone-equivalent (17,44,45).

1.3.4 Corticoids and IFN signature

SLE is an autoimmune disease characterised by chronic stimulation of the innate immune system by endogenous nucleic acids. The hallmark of the SLE disease is an increased IFN (interferon) signature in the blood which is an increased expression of type I IFN-regulated genes (such as IFN α) and it is tightly associated with levels of autoantibodies and disease activity. Self-nucleic acid recognition by

Toll like receptor (TLR) 7 and TLR9 on B cells and PDC (plasmacytoid dendritic cells) is believed to be the key in the pathogenesis of SLE promoting immune complexes (IC) and the production of type I IFN. PDCs migrate then from the blood into inflamed tissues including the kidney. I IFN promotes T cell activation, autoantibody production by B cells and the release of neutrophil extracellular traps (NETs) that consist of immune complexes that are preferentially endocytosed by pDCs via Fc receptors (46–48).

The pathogenic role of type I IFNs was provided by Ronnblom and colleagues when they demonstrated that elevated serum IFN- α levels could be driven by immune complexes. In their study, IFN was produced when immunoglobulin from patients with SLE was combined with plasmid DNA or apoptotic cells and added to peripheral blood mononuclear cells (PBmCs) (48–50). Blanco et al. showed that SLE patients serum had the capacity to induce the maturation of monocytes into DCs in an IFN- α -dependent manner. DC differentiation into antigen presenting cells was correlated with disease activity and depended on the actions IFN- α (51). Richez et al. showed another pathway for IFN- α production during the exacerbation of disease in SLE, in a context of bacterial infection: in a mouse model DCs and human monocytes produce abundant IFN- α following TLR4 engagement, which binds bacterial lipopolysaccharide (LPS), if the cells have been pre-treated either with IFN- β , or with supernatant from DCs activated by RNA-containing immune complexes from lupus patients (52).

A recent study suggests that the IFN pathway was not affected in patients treated by oral GCs and only intravenous pulse therapy can normalise the IFN signature. This was correlated with a reduction in PDCs. The inhibition of the IFN-signature by pulse therapy is transient, returning to pre-pulse levels 8 days later (42).

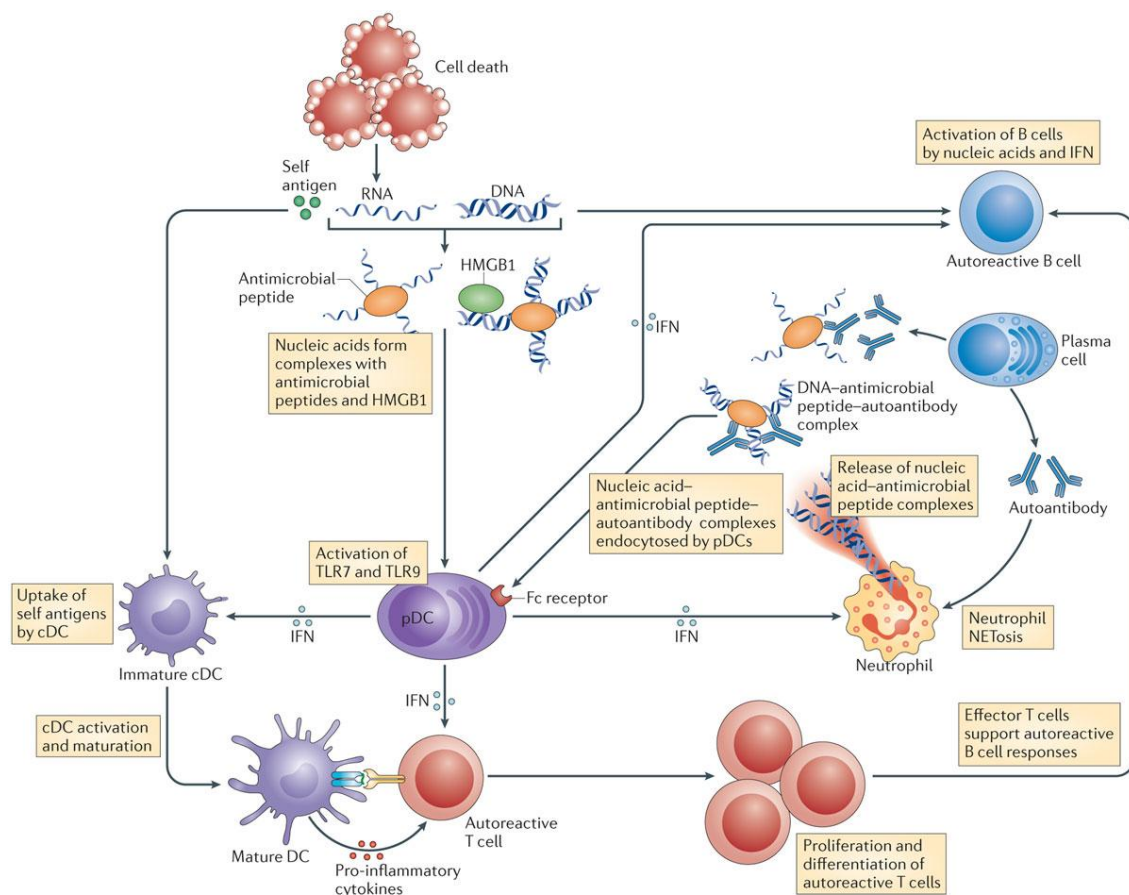


Figure 3: The production of type I IFN by pDCs as a common mechanism of pathogenesis of SLE adapted from Ganguly et al (47).

2. Glucocorticoids are recommended in the treatment of lupus nephritis

The treatment of lupus nephritis has changed significantly over the past decade. We will try to summarise and discuss the currently available standard of care GCs treatments for severe LN, focusing on class III (focal proliferative), class IV (diffuse proliferative) and class V (membranous) lupus glomerulopathy.

The objective of treatment for active lupus nephritis is to preserve nephrons by reversing the acute inflammatory process and achieving a state of disease quiescence. The concept of two phases of therapy: first induction then maintenance is widely accepted (3). So the management of patients with active lupus nephritis comprises two parts: in patients with active disease, potent immunosuppressive medications including high-dose of GCs are administered with the objective of inducing rapid disease quiescence, referred to as the induction phase. A long-term maintenance therapy follows, in which immunosuppressive medications are used at reduced doses to maintain a stable state and prevent further renal flares. Thanks to the selection of treatment and their doses, physicians try to minimise treatment-related adverse effects and should, therefore, include a long-term perspective and take into account a fine balance between efficacy and risk considerations (2).

The current guidelines are European (EULAR - ERA EDTA - European League Against Rheumatism, European renal association - European dialysis and transplant association), American (ACR- American College of Rheumatology) and internationally based with the addition of the KDIGO (Kidney Disease Improving Global Outcomes) guideline that is considered to be international. Over the past decade, several randomised controlled trials have been conducted for Class III and IV LN, both in the induction and in the maintenance phase with many clinical trials using GCs as standard-of-care therapy in association with immunosuppressive agents (53,54). All guidelines were published within the same period and based on the same body of evidence, and their main statements are congruent and uniform. However, notable differences between them persist (54). The guidelines offer information on different aspects of the management of lupus nephritis including induction and maintenance treatment of the different histological classes but little is specified concerning doses of GCs, either for pulses, or for oral GCs and even less to guide the rate of tapering, the total duration or the minimal effective dose of initial and ongoing GCs therapy (54,55).

2.1 Induction therapy

Current standard of care induction therapy for active, severe proliferative or membranous lupus nephropathy is dual immunosuppression usually an immunosuppressive agent in combination with oral GCs with or without three pulses of intravenous high-dose methylprednisolone (MP) at start of induction treatment (2,54). The use of pulse MP at induction is not always recommended and is reserved by some of the guidelines for more severe cases (54). GCs still remain the standard of care in this case and has been recommended by many scientific societies (56–58).

2.1.1 GCs induction therapy for Class III-IV Lupus nephritis

Generally, induction treatment for class III–IV lupus nephritis should combined immunosuppression with high-dose corticosteroids and an immunosuppressive agent usually either mycophenolate mofetil (MMF) or cyclophosphamide (CYC).

Therefore proliferative lupus nephritis should initially be treated with a pulse of intravenous GCs: usually methylprednisolone for 3 consecutive days, followed by a high-dose GCs oral regimen. Although, in general, the use of both oral and intravenous GCs has been proven effective, evidence is scarce concerning dose and duration and recommendations are mainly based on expert opinions.

In the guidelines, the dose of initial MP pulses varies from 500 to 1000 mg/day. The experts recommend one daily MP pulse for up to 3 consecutive days, but the Europeans allow more pulses if required. Concerning the initial dose of oral GCs, dose varies from 0.5 to 1.0 mg/kg/day. However,

there is a variability of opinion on the use of pulse steroid therapy and its optimal dose in patients with less aggressive disease (2,3,54,56–58).

2.1.2 GCs induction therapy for LN Class V

Initial immunosuppression for patients with severe manifestations, especially those who present a nephrotic range proteinuria (>3 g/24 h) should be oral GCs, combined with an immunosuppressive therapy either mycophenolate mofetil or cyclophosphamide, or oral GCs combined with a calcineurin inhibitor (2,56–58). There is also no consensus neither on the daily doses of GCs nor on its duration, although there is agreement that GCs should be included in the regimen (54,56–58).

2.1.3 GCs tapering after induction therapy

There is a lack of clarity over the duration of this treatment, and it is also unclear when to start reducing the dose and what dose should be reached. Furthermore, advice for tapering of GCs is usually fairly general, even if all the scientific societies agree that the dose should be gradually reduced as soon as the clinical conditions allow it in order to reach an effective minimal dose for controlling the disease (2,3,54,56–58).

2.1.4 Summary of the current recommendations for the use of Glucocorticoids in Lupus Nephritis in Induction Therapy

- **ACR:** American College of Rheumatology
- **EULAR:** European League Against Rheumatism
- **ERA-EDTA:** European renal association - European dialysis and transplant association
- **KDIGO:** Kidney Disease: Improving Global Outcomes
- **PNDS –HAS:** Protocol national de diagnostic et de Soins, Haute autorité de santé ; French National Diagnostic and Care Protocol.

Table 1 - Recommendations for Focal proliferative Lupus Nephritis Class III & Diffuse proliferative Lupus nephritis class IV

Scientific Society	IV GCs	Oral GCs	Tapering	Level of recommendations
ACR 2012 <i>Guidelines for Treatment and Management of Lupus Nephritis (58)</i>	Daily Pulses IV GCs: <ul style="list-style-type: none"> - IV Methylprednisolone - 500–1000 mg/day - For 3 doses 	IV GCs pulses should be relayed by <ul style="list-style-type: none"> - Daily oral GCs - 0.5-1 mg/kg/day 	<ul style="list-style-type: none"> - Oral GCs should be followed by a taper to the minimal amount necessary to control disease. - Insufficient data to recommend a specific steroid taper. 	Level C
EULAR/ERA-EDTA 2012 <i>Recommendations for the management of adult and paediatric lupus nephritis (59)</i>	Daily Pulses IV GCs: <ul style="list-style-type: none"> - IV Methylprednisolone (MP) - three consecutive pulses of IV MP - 500–750 mg <p>Further course of three intravenous MP pulses can be considered in patients failing to improve within the first 3 months.</p>	IV GCs pulses should be relayed by <ul style="list-style-type: none"> - Oral prednisone - 0.5 mg/kg/day - for 4 weeks - Tapering to ≤10 mg/day by 4–6 months <p>Higher doses of oral prednisone (0.7–1 mg/kg/day) may be used in severe renal or extra-renal lupus, or when intravenous MP treatment is not feasible.</p>	Oral GCs should be reduced to ≤10 mg/day by 4–6 months	Level C
EULAR 2013 <i>Recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases (57)</i>	No specific recommendation on IV GCs	Recommendations only for medium to high-dose (ie, >7.5 mg but ≤100 mg) prednisone equivalent daily. Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment	Keep the requirement for continuing GCs treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment and development of adverse events	Percentage of the task force members that strongly to fully recommended this proposition: 92%

Table 1 - Recommendations for Focal proliferative Lupus Nephritis Class III & Diffuse proliferative Lupus nephritis class IV

Scientific Society	IV GCs	Oral GCs	Tapering	Level of recommendations
KDIGO 2012 Clinical Practice Guideline for Glomerulonephritis (56)	<ul style="list-style-type: none"> - Additional IV methylprednisolone is widely used at the beginning of treatment for severe disease. - No recommendation on duration and doses 	Initial dose of oral prednisone up to 1 mg/kg/day	Tapering of GCs according to clinical response over 6–12 months.	Level 1A
French Guidelines 2010 Systemic Lupus Erythematosus, National Diagnostic and Care Protocol PNDS –HAS (60)	<ul style="list-style-type: none"> - Therapy may be initiated by infusion of 500 or 1000 mg of IV methylprednisolone - Often for 3 consecutive days, then relieved by oral corticosteroid therapy. 	<ul style="list-style-type: none"> - Treat with high-dose corticosteroid therapy, but there is no clear pattern for corticosteroid therapy. The reference corticosteroid is prednisone (AMM). - Initial dose and duration are guided by the severity factors at the time of diagnosis (most commonly prednisone 1 mg/kg/day for 3 to 4 weeks). 	<ul style="list-style-type: none"> - The decrease must then be progressive. - Usually, 10% decrease in the previous dose every 10 to 15 days, or 2.5 mg every 2 weeks. 	Not defined

Table 2 - Recommendations for Lupus Nephritis Class IV or IV/V with cellular crescents

Scientific Society	IV GCs	Oral GCs	Tapering	Level of recommendations
ACR 2012 <i>Guidelines for Treatment and Management of Lupus Nephritis (58)</i>	Pulses IV GCs: - High doses - no recommended duration	Iv pulses relayed by - daily oral GCs - higher range dose - 1 mg/kg/day	No recommendation	Level C

Table 3 - Recommendations for Membranous Lupus Nephritis Class V

Scientific Society	IV GCs	Oral GCs	Tapering	Level of recommendations
ACR 2012 <i>Guidelines for Treatment and Management of Lupus Nephritis (58)</i>	No recommendation	In case of nephrotic range proteinuria only: - prednisone - 0.5 mg/kg/day - for 6 months	No recommendation	Level A
EULAR/ERA-EDTA 2012 <i>Recommendations for the management of adult and paediatric lupus nephritis (59)</i>	No recommendation	Oral prednisone (0.5 mg/kg/day)	No recommendation	Agreement level among experts : 9/10
KDIGO 2012 Clinical Practice Guideline for Glomerulonephritis (56)	No recommendation	In case of persistent nephrotic proteinuria, treat with corticosteroids.	No recommendation	Level 2D
French Guidelines 2010 Systemic Lupus Erythematosus, National Diagnostic and Care Protocol PNDs –HAS (60)	No recommendation	In case of persistent nephrotic proteinuria, treat with prednisone, 0,5 to 1 mg/kg/day during 1 month and then taper.	Taper after 1 month of oral GCs therapy.	Not defined

2.2 Maintenance therapy

2.2.1 Glucocorticoids and maintenance therapy

Once remission has been induced, maintenance phase therapy should focus on the long-term management of chronic, more or less indolent, disease. GCs remain a major component of treatment in the maintenance phase of lupus nephritis therapy: the current recommendations are based on clinical studies that do not exclude the use of steroids in maintenance therapy (3).

In the maintenance phase of treatment, either mycophenolate or azathioprine is recommended by all guidelines, supported by low-dose oral GCs, but without any consensus concerning the optimal dose, if tapering is needed or the optimal duration (2,56–58). The EULAR committee recommends judicious use of these agents, taking into consideration the potential harms associated with these drugs (59,61). Finally, with respect to the duration of the treatment, guidelines differ: at least 3 years (EULAR/ERA-EDTA) or at least 1 year (KDIGO) after (complete) remission. Due to the length of completed studies, there is no advice on the optimal duration of therapy beyond 3 years (54,56–58).

2.2.2 Summary of the current recommendations for the use of Glucocorticoids in Lupus Nephritis in Maintenance Therapy

Table 4 - Recommendations for maintenance therapy

Scientific Society	IV GCs	Oral GCs	Tapering	Level of recommendations
ACR 2012 <i>Guidelines for Treatment and Management of Lupus Nephritis (58)</i>	No recommendation	Low dose oral GCs	No recommendation	Not defined
EULAR/ERA-EDTA 2012 <i>Recommendations for the management of adult and paediatric lupus nephritis (59)</i>	No recommendation	Low dose prednisone (5 to 7.5 mg/day)	<ul style="list-style-type: none"> - There is no data to guide duration of treatment beyond 3 years - Continuing treatment for longer time periods should be individualised with an effort first to withdraw glucocorticoids before immunosuppressive agents. 	Level C
EULAR 2007 <i>Recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases (61)</i>	No recommendation	No recommendation	<ul style="list-style-type: none"> - For prolonged treatment, the GCs dosage should be kept to a minimum - A GCs taper should be attempted in case of remission or low disease activity 	Percentage of the task force members that strongly to fully recommended this proposition: 86%
KDIGO 2012 <i>Clinical Practice Guideline for Glomerulonephritis (56)</i>	No recommendation	<ul style="list-style-type: none"> - Low-dose oral corticosteroids - ≤ 10 mg/day prednisone equivalent 	Maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression	Oral GCs: Level 1B Tapering: Level 2D
French Guidelines 2010 <i>Systemic Lupus Erythematosus, National Diagnostic and Care Protocol PND5 –HAS (60)</i>	No recommendation	No recommendation	<ul style="list-style-type: none"> - Low doses of GCs (5-10mg/day of prednisone) may be maintained over long term - Maintenance corticosteroids (5 mg/day or 0.10 to 0.20 mg/kg/day) are often maintained for several years, depending on the initial severity or any previous relapses. - The optimal duration of maintenance treatment is not defined. The current trend is the extension of maintenance treatment for a period of 5 years. 	Level A

3. Adverse effects of steroids

GCs remains the corner stone treatment and most of SLE patients have received GCs; in some cohorts up to 80% of patients continue indefinitely this treatment as “maintenance” therapy, at low doses of less than 7.5 mg/day. This long-term treatment results in various side effects and contributes to worsen quality of life even years after its withdrawal. Although the risk of side effects is dependent on time and dose and the cumulative dose of GCs is clearly related to adverse effects, intermittent or low dose therapies have also been associated with damages (13,62,63).

In fact GCs use is associated with several significant side effects like osteoporosis, metabolic syndrome, cardiovascular disease, infections, osteonecrosis, myopathy and cataracts, among others (17,62,64,65).

3.1 Glucocorticoids & Bone health

3.1.1 Glucocorticoids & Osteoporosis

GCs therapy results in an early and rapid bone loss and increased fracture risk after beginning of GCs treat. GCs acting through bone GR increase life span of osteoclasts and induce osteocyte apoptosis and decrease bone remodeling. There is an early deleterious effect of GCs that persists throughout the duration of GCs therapy on bone with a transient increase in bone resorption followed by a decrease in bone formation. Osteogenesis is also suppressed leading to bone collapse. Indirect effects of GCs also occur as a result of hypogonadism, decreased intestinal calcium absorption and reduce renal calcium reabsorption, increased intestinal and renal calcium loss and vitamin D insufficiency because of accelerated catabolism of 25(OH)D and 1,25(OH)₂D due to GCs (62).

Fracture risk is dose dependent but it increases even with low dose (2.5–7.5 mg of prednisolone or the equivalent) or intermittent therapy (62,66,67). Carli and al showed on univariate analysis that cumulative doses of GCs were correlated with osteoporosis (OP) ($p < 0.03$) (67). Fractures in glucocorticoid induced OP occurs independently of bone mass density (BMD) and can be found in up to 30–50% of patients (62,66). A Spanish study has determined the prevalence of undiagnosed vertebral fractures in women chronically using GCs therapy for auto immune disease : Morphometric vertebral fractures were detected in 13.7 % of SLE patients, 4-times more frequently than self-reported by patients (3.2 %) (68).

3.1.2 Glucocorticoids & Osteonecrosis

Up to 40% of patients can present non traumatic osteonecrosis after long-term GCs therapy. The risk increases with higher doses and prolonged treatment but it may also occur with short-term exposure to high doses (62,64,66). In a recent systematic review of the literature including fifty-seven studies (23,561 patients) it has been reported that osteonecrosis incidence was 6.7% with corticosteroid treatment of >2 g (prednisone-equivalent) and that SLE patients had positive correlations between dose and osteonecrosis incidence. Each 10 mg/day increase was associated with a 3.6% increase in osteonecrosis rate, and >20 mg/day resulted in a higher osteonecrosis incidence. Mean osteonecrosis incidence was 33% in twenty studies evaluating the effects of pulsed corticosteroids based on data from the systematic review (69). The effects of GCs on bone density loss are thought to be rapid with medication initiation, then slower after 6 months of treatment. After withdrawal of GCs therapy, fracture risk returns partially back to baseline levels. Unless the patient had substantial loss in bone mass due to high cumulative doses of GC the risk remains higher (62,66).

3.2 Glucocorticoids & Cardiovascular Events

Patients with SLE are at excess risk of cardiovascular events (CVEs). Reports have suggested that this higher risk is multifactorial, with contributions from traditional risk factors for CVEs, SLE disease

activity, SLE-related immunologic factors (recent levels of circulating anti-double-stranded DNA, positive antiphospholipid antibody (aPL), elevated markers of endothelial activation (von Willebrand factor (vWf), soluble vascular cellular adhesion molecule-1 (sVCAM-1) and fibrinogen), and SLE-related medications such as GCs (70–72). GCs major numerous cardiovascular risk factors like obesity, insulin resistance, glucose intolerance, dyslipidaemia and hypertension. GCs promote atherogenesis and affect vascular remodeling and have direct effects on the heart, kidneys and blood vessels, influence vascular function. The risk is related to the development of an exaggerated metabolic syndrome (17,62).

The glucocorticoids are a primary factor that influences cardiovascular risk. There is a directly proportional relationship between the cumulative GCs dose and the increase in cardiovascular risk with SLE patients(73). Magder and Petri showed that doses of prednisone more than 10 mg per day were associated with a two-fold increased risk and more than 20 mg with a five-fold increased risk. This remained true after adjusting for disease activity (70). The cumulative dose of GCs promote hypertriglyceridemia and insulin resistance and are associated with a higher cholesterol plasma level, higher blood pressure and weight change in lupus patients (74). Petri and al. showed that increases in prednisone dose in SLE patient led to definable changes in risk factors for coronary artery disease, a change in prednisone dose of 10 mg and the duration even at this level was associated with a change in cholesterol (75). Wei et al. found a 2.56-fold increase in risk of cardiovascular events with a prednisone dose of 7.5 mg or more. In the Hopkins Lupus Cohort, an increase in prednisone dose of 10 mg caused an increase in cholesterol of 7.5 mg/dL, weight change of 5.5 lbs and change in blood pressure of 1.1 mmHg (76,77). An ongoing excess cardiovascular risk is sustained after cessation of exogenous GCs administration. Current use or even a past use of GCs increased significantly the risk for heart failure. This might be explained by the mineralo-corticoid effects of GCs which increases sodium and fluid retention and promotes remodeling through fibrosis of the atria and ventricles (62).

3.3 Glucocorticoids & Infections

GCs exert many immunosuppressive effects that induce cellular immunodeficiency and consequently increase host susceptibility to a wide variety of infectious pathogens: bacterial infections are most frequent, followed by viral, then fungal and parasitic infections and also predisposed to opportunistic infections. Infection is well recognised to be a cause of early and late deaths in lupus (62,78–81).

The risk is associated with daily dose and duration of therapy; some studies highlighted the importance of the cumulative dose. Numerous studies have demonstrated that corticosteroids, already with prednisone doses over 7.5-10 mg/day and especially in doses higher than prednisone 20 mg daily (or its equivalent), and also when administered intravenously, significantly increased susceptibility to infection (3,5,9,36–38). A recent cohort study confirmed that damage due to steroids increased over the five years of follow-up while damage independent of steroids therapy remained constant throughout the period of observation (82). Also, concerning infection, the risk decreases after withdrawal of GCs. Limiting steroid administration for less than 21 days also decreases infectious complications (62,78,79,83–90).

3.4 Glucocorticoids & Morbidity Mortality in SLE

Several longitudinal studies performed in SLE patients have revealed that GCs were the main cause of damage and sequelae, as determined by the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (91).

Thus the mean SLICC/ACR damage index (SDI) rose from 0.33 at baseline to 1.9 after 15 years of follow-up in an inception cohort, and damage was considered as GCs-related in 16% and 49% of the cases at baseline and last follow-up, respectively (92). Ruiz-Arruza et al. showed that mean doses of

prednisone >7.5 mg/day increased the risk of accruing damage after 5 years of follow-up, whilst doses <7.5 mg/day and methylprednisolone pulses did not (93).

Finally, damage accrual was found to be associated with higher risk of mortality, every 1-point increase in SDI being associated with a 1.32 times more risk to die during follow-up (81).

4. Treat lupus with lower doses or without Glucocorticoids

Due to the considerable side effects of GCs, both patients and physicians are concerned with the use of GCs and there is an urgent need to find new protocol to avoid a prolonged cortisonic impregnation and to reduce the doses of GCs. Research team have been focusing on defining new treatments which minimise therapy related toxicity and reduce in particular the burden of steroid use.

The paradigm of immunosuppressive treatment for lupus nephritis has evolved over the past few decades from corticosteroids alone to corticosteroids combined with immunosuppressants and now to immunosuppressants alone or with less GCs.

4.1 Reduce the doses of GCs

Is reducing or stopping corticosteroids an achievable and reasonable goal? In order to limit GCs toxicity, lower oral doses have been successfully used in lupus nephritis trials in association with other immunosuppressants, such as azathioprine, mycophenolate mofetil or cyclophosphamide, widely used as steroid sparing agents (94).

First indications are given by Zahr et al. who reported on the largest prospective cohort study of predictors of prednisone tapering in SLE patients. This Hopkins Lupus Cohort gathered 866 patients from 1987 through 2009. The analysis was based on patients whose previous prescribed dose of prednisone was 5 mg/day. The authors examined the proportion of times the patient's dose was reduced to below 5 mg/day. Among those patients who tapered oral GCs they analysed the proportion whose prednisone dose remained below 5 mg/day for at least one year.

The analyses showed that Caucasians, younger patients, patients with a higher level of education, lower disease activity, or absence of urine protein were more likely to have a prednisone taper. However, successful tapering, so patients who were treated during at least one year with a dose of prednisone under 5mg/day was not dependent on age, ethnicity, or education but it was more frequent in those with lower disease activity. Successful tapering was achieved more often after the year 2000 (95).

Pr. Ruiz-Irastorza and his team from Bilbao proposed a specific new therapeutic scheme in order to spare oral GCs, the Cruces-protocol cohort (CC) (96). The patients from the CC received medium doses of prednisone (Class II up to 15mg/day, Class III-IV up to 20-30mg/day, Class V up to 15mg/day), combined with methyl-prednisolone pulses (3 consecutive days bolus from 250mg to 500mg and one methylprednisolone 125 or 250 mg pulse was given just before each dose of cyclophosphamide), hydroxychloroquine (HCQ) and immunosuppressive drugs, usually cyclophosphamide. The oral dose of GCs was quickly tapered every 2 weeks until 10 mg/day (class III and IV) or 7.5 mg/day (class II and V), being then reduced by 2.5 mg/day every 4 weeks to a maintenance dose of 2.5–5mg/day. These patients were compared to the historic cohort (HC) who received high-dose prednisone (up to 1mg/kg/day) and followed a NIH (National Institutes of Health) protocol-based scheme (cyclophosphamide for class III and IV or azathioprine or mycophenolate mofetil for others states).

Among the forty-five patients included in the analysis, the CC patients were less exposed to oral GCs and tapering to 5mg/d was quicker. The mean (SD) cumulative doses of prednisone at six months were 1.7 (0.5) g vs. 4.5 (2.1) g ($p < 0.001$), in the CC and HC, respectively, which resulted in average doses of 9 mg/d and 25 mg/d, respectively. Furthermore the mean (SD) weeks to achieve the

reduction of prednisone to 5 mg/day were 16 (± 9) weeks in the CC vs. 130 (± 146) weeks in the HC ($p < 0.001$). This CC protocol is at least as effective in achieving remission of LN as regimes containing high-dose prednisone. But this protocol causes less toxicity: Global toxicity attributable to GCs was seen in 1/15 patients (7%) in the CC vs. 20/30 patients (67%) in the HC ($p < 0.0001$) (96).

The duration of corticosteroid administration during maintenance therapy in LN remains controversial and non evidence-based. A small pilot study by Galbraith et al. was achieved in order to assess the feasibility of doing a larger trial on whether maintenance corticosteroids are needed in LN. This study included 15 patients with proliferative (membranous) LN induced with cyclophosphamide or MMF who achieved at least a partial response and had been tapered down to 20 mg of prednisone. Patients were randomised to prednisone continuation with low-dose maintenance target (5-7.5 mg/day) ($n=8$) or to withdrawal ($n=7$). Patients were followed for a median of 11.9 months, and the end point was renal or major non-renal relapse. Relapse occurred in only one patient from the withdrawal group (14%; one renal flare), but in 50% of the low-dose prednisone patients (three renal flares and one major non renal flare) (97).

4.2 The new wave: Treat without oral GCs

Avoiding oral steroids in the treatment of LN is now the aim. Rituximab might also be effective without long-term corticosteroids. A London research team led by Pr. Liz Lightstone from the Imperial College has piloted a steroid-avoiding protocol (RITUXILUP) for the treatment of biopsy-proven active International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III, IV, or class V LN. In this open-label trial, 50 patients with LN who were not taking long-term oral steroids, were treated with two doses of rituximab (1 g infusion every two weeks) together with intravenous methylprednisolone 500 mg and mycophenolate mofetil at a starting dose of 1 g daily, titrated to achieve a maximum dose of 3 g daily but without any oral GCs. At 52 weeks, the complete response and partial response rates were 52% and 34%, respectively. Patients with class III, IV or V lupus nephritis responded similarly. Adverse events were infrequent, with hospital admission and infection occurring in 18% and 10% of the patients, respectively (98).

Following this study, this regimen is currently tested in a phase III open label randomised multicentre controlled trial against conventional treatment protocol in the ongoing RITUXILUP (Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis) that aims to demonstrate whether the addition of Rituximab to MMF therapy is useful in treating a new flare of lupus nephritis and whether it has a long lasting steroid-sparing, beneficial effect with equal efficacy and greater safety than a conventional regimen of MMF and oral prednisolone. Estimated study completion is expected for April 2019 (94,99).

CORTICOLUP is a French ongoing study which objective is to study the possibility of corticosteroids interruption in patients with quiescent SLE treated since at least one year with 5 mg of prednisone per day. The primary outcomes are the occurrence of mild or moderate flares of SLE. The estimated Study Completion is expected for April 2018 (100).

II. Suggested Study: A collaboration between Bordeaux & Bilbao

1. OBJECTIVE

The suggested study is a multicentre observational retrospective study whose objective is to compare the effectiveness and safety of a protocol following mainly the international guidelines (“Bordeaux Cohort”) to a protocol using different doses of GCs with a specific GCs tapering regimen (“Cruces-protocol cohort”) to treat lupus nephritis (class III, IV and V).

2. METHODS

Patients with lupus nephritis from the “Cruces-protocol cohort” (CC) were compared with patients from the “Bordeaux cohort” (BC).

Partial and complete remission rates and glucocorticoid-related toxicity were assessed at 6 and 12 months.

2.1 Cruces-protocol protocol

The CC uses medium doses of prednisone combined with methyl-prednisolone pulses, HCQ and immunosuppressive drugs, usually cyclophosphamide. To sum up, starting doses of prednisone range between 15 and 30 mg/day depending on LN class and clinical status. This dose is quickly tapered every 2 weeks until 10 mg/day (class III and IV) or 7.5 mg/day (class II and V), being then reduced by 2.5 mg/day every 4 weeks to a maintenance dose of 2.5–5 mg/day.

For class III and IV, the induction treatment starts with three consecutive daily intravenous methyl-prednisolone pulses of 250–500 mg. Then, 6 to 12 fortnightly intravenous pulses of 500 mg of cyclophosphamide are administered, the final number depending on renal response.

Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are used as needed according to blood pressure and the degree of proteinuria. All patients were prescribed calcium and vitamin D.

2.2 Bordeaux protocol

In the Bordeaux cohort, patients are treated according current guidelines.

Most patients with proliferative forms are treated according to the Euro-Lupus Nephritis Trial using low doses of intravenous cyclophosphamide (6 pulses at a fixed dose of 500 mg, given at 2-week intervals) with pulses of methylprednisolone (1 to 3) at the induction therapy. Patients with class V LN are mostly treated with mycophenolate mofetil.

In all cases, oral prednisone or prednisolone are generally initiated at a dose of 0.7–1.0 mg/kg body weight daily and reduced by 2.5–5.0 mg every 2 to 4 weeks until the long-term maintenance dose is reached.

Maintenance therapy usually includes low-dose GCs (5 - 7,5 mg prednisone/day) and azathioprine or mycophenolate mofetil for many years.

Regarding HCQ, antiproteinuric agents and calcium and vitamin D, the decision of whether to prescribe these drugs are dependent on an eventual contraindication and the choice of the attending physician.

2.3 Definition of remission

Complete remission was defined as a GFR ≥ 60 ml/min/1.73 m² (or return to initial GFR or $\pm 15\%$ to the initial value in those with GFR < 60 ml/min/1.73 m² at diagnosis), proteinuria ≤ 0.5 g/24 h, inactive

sediment (≤ 5 red blood cells, ≤ 5 leucocytes and absence of hematic casts) and serum albumin > 3 g/dl.

Partial remission was defined as a decrease in proteinuria below 3.5 g/24 h in patients with initial nephrotic proteinuria or $> 50\%$ reduction of proteinuria in those with initial values below 3.5 g/24 h; in both cases, with stabilisation ($\pm 25\%$) or improvement in the baseline GFR.

3. OUTCOMES

The main outcomes were complete renal remission (CR) and toxicity secondary to glucocorticoids. Univariate comparisons and multivariate Cox regression analysis were used.

4. RESULTS

The mean maximum prednisone dose was 42.5 mg/day in the BC vs. 21.2 mg/day in the CC ($p < 0.001$). The average prednisone dose within 6 months was 21 mg/day in the BC vs. 8.3 mg/day in the CC ($p < 0.001$). The mean number of methylprednisolone pulses was 2.3 in the BC vs. 9.3 in the CC ($p < 0.001$). HCQ was used by 63.64% in the BC vs. 100% in the CC ($p < 0.001$).

CR rates were 30.2% in the BC vs. 69% in the CC ($p = 0.001$) and 43% in the BC vs. 86% in the CC ($p < 0.001$) at 6 and 12 months, respectively. Patients from the CC more frequently achieved CR (adjusted HR 3.8, 95%CI 2.05-7.09). The number of pulses of methylprednisolone was associated with CR (adjusted HR 1.09, 95%CI 1.03-1.15). Patients in the CC had a lower risk of GC-related side effects (adjusted HR 0.19, 95%CI 0.04-0.89).

5. CONCLUSION

The Lupus-Cruces nephritis protocol improves the outcome of LN.

6. SUPPLEMENTARY DATA

6.1 Details of the treatments received in BC

6.1.1 Induction therapy received in BC

23 patients with severe proliferative forms of LN were treated with EUROLUPUS protocol-based scheme: 10 patients with LN class III, 12 patients with LN class IV and 1 patient with LN class IV-V. In this case patients received every two weeks low dose cyclophosphamide pulses therapy (500mg) during 3 months. This induction therapy was associated with three consecutive daily intravenous methylprednisolone pulses for 20 patients, 2 pulses for 1 patient and more than 3 pulses for 2 patients (up to 6 pulses), ranging from 120mg/day to 1000mg/day according to the physician.

Two patients with LN class III or IV followed a NIH protocol (0.5-1.0g IV Cyclophosphamide monthly).

12 patients received mycophenolate mofetil (Cellcept) as induction therapy: 6 patients with LN class III, 4 patients with LN class IV and 2 patients with LN class 2.

Finally 7 patients (3 LN class III, 4 LN class IV) who all presented a recurrence of their renal disease were treated with rituximab (Mabthera).

Oral GCs received in BC

Regarding oral GCs, prednisone was given usually at high doses (1 mg/kg/d) with variable duration and tapering scheme, according to the discretion of the treating physicians. Most of the patients (31) received an initial GCs dose ≥ 0.5 mg/kg/day.

Summary of the Induction therapy received in BC

Table 5- Immunosuppressant Induction therapy received in BC

Immunosuppressant induction therapy	Total of patients	LN class III (n)	LN class IV (n)	LN class V (n)	First renal flares (n)	Renal recurrence (n)
Eurolupus Protocol	23	10	12	1 patient class IV and V	15	8
NIH Protocol	2	1	1	0	0	2
Mycophenolate Mofetil	12	6	4	2	4	8
Rituximab	7	3	4	0	0	7

Table 6 - Glucocorticoids Induction Therapy received in BC

GCs induction therapy	Total of patients	LN class III (n)	LN class IV (n)	LN class V (n)	First renal flares (n)	Renal recurrence (n)
Boli IV Methylprednisolone	32	13	18	1	18	14
0-2 boli MP	1		1			1
3 boli MP	29	13	16		16	13
>3 boli MP	2		1	1	2	
No IV GC	11	6	3	2	3	8
Oral GCs (as induction therapy or as relay of IV GCs pulses)	42	20	21	1	22	20
Initial dose oral GCs <0.5mg/kg/d	11	7	2		3	8
Initial dose oral GCs ≥0.5mg/kg/d	31	13	17	1	18	19

To note: 2 patients had no oral GCs initially. For 1 patient we couldn't verify the number of GCs boli.

6.1.2 Maintenance therapy received in BC

Maintenance therapy usually included oral GCs (prednisone) and azathioprine or mycophenolate mofetil.

Only two patients stopped oral GCs at 6 months and a total of 14 patients had no GCs at the end of the follow-up.

At the opposite 39 patients still had oral GCs at 6 months and 30 patients still had oral GCs at the end of the follow-up. Most patients had oral GCs $\geq 5\text{mg/d}$, respectively 38 patients at 6 months and 20 patients at the end of the follow-up. Low-dose oral GCs $< 5\text{mg/d}$ concern only 1 patient at 6 months and 10 patients at the end of the follow-up.

We could not determine the posology of GCs at the end of the follow-up for 3 patients.

Summary of the maintenance therapy received in BC

Table 7 - Glucocorticoids maintenance therapy received in BC

GCs maintenance therapy	Total of patients	LN class III (n)	LN class IV (n)	LN class V (n)	First renal flares (n)	Renal recurrence (n)
No oral GCs at 6 months	2		1	1		2
Oral GCs < 5mg/d at 6 months	1	1			1	
Oral GCs ≥ 5mg/d at 6 months	38	17	20	1	20	18
No oral GCs at the end of the follow-up	14	7	6	1	7	7
Oral GCs < 5mg/d at the end of the follow-up	10	4	6		7	3
Oral GCs ≥ 5mg/d at the end of the follow-up	20	10	9	1	8	12

To note: We could not determine the posology of Gcs at the end of the follow-up for 3 patients. We couldn't determine the periode with a dose ≥ 5mg/d for two patients.

REPEATED PULSES OF METHYL-PREDNISOLONE WITH REDUCED DOSES OF
PREDNISONE IMPROVE THE OUTCOME OF CLASS III, IV AND V LUPUS
NEPHRITIS: AN OBSERVATIONAL COMPARATIVE STUDY OF THE LUPUS-CRUCES
AND LUPUS-BORDEAUX COHORTS.

GUILLERMO RUIZ-IRASTORZA (1)

AMAIA UGARTE (1)

CECILE SAINT-PASTOU TERRIER (2)

ESTIBALIZ LAZARO (2,3)

AMALUR IZA (1)

LIONEL COUZI (3,4)

RAMON SAENZ (1)

CHRISTOPHE RICHEZ (3,5)

SABRINA PORTA (1,6)

PATRICK BLANCO (3,7)

1.- Autoimmune Diseases Research Unit, Department of Internal Medicine, Biocruces Health Research Institute, Hospital Universitario Cruces, UPV/EHU, Bizkaia, The Basque Country, Spain.

2.- Internal Medicine Department, FHU ACRONIM, Haut-Lévêque Hospital, Bordeaux, France.

3.- UMR CNRS 5164, ImmunoconcepT, Bordeaux University, Bordeaux, France.

4.- Nephrology Department, FHU ACRONIM, Pellegrin Hospital, Bordeaux, France. 0556795679

5.- Rheumatology Department, FHU ACRONIM, Pellegrin Hospital, Bordeaux, France.

6.- Rheumatology Department, Hospital J.M Ramos Mejía, Buenos Aires, Argentina

7.- Immunology department, FHU ACRONIM, Pellegrin Hospital, Bordeaux, France.

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CORRESPONDING AUTHOR:

Guillermo Ruiz-Irastorza

Unidad de Enfermedades Autoinmunes

Hospital Universitario Cruces

48903-Bizkaia

Spain

ABSTRACT:

OBJECTIVE: To compare the clinical course of patients with class III, IV and V lupus nephritis (LN) treated at Hospital Universitario Cruces (CC) and at Bordeaux University Hospital (BC).

METHODS: The Lupus-Cruces nephritis protocol combines pulses of 125 mg of methyl-prednisolone with each fortnightly pulse of cyclophosphamide and prednisone ≤ 30 mg/day with tapering over 12-14 weeks until 2.5-5 mg/day. The BC followed international lupus nephritis guidelines, combining high-dose prednisone and either mycophenolate mofetil or cyclophosphamide, followed by maintenance therapy with low dose prednisone and immunosuppressive drugs. The main outcomes were complete renal remission (CR) and glucocorticoid toxicity.

RESULTS: 44 patients from BC and 29 CC were included. The mean maximum prednisone dose was 42.5 (BC) vs. 21 mg/day (CC), $p < 0.001$. The average 6-month prednisone dose was 21 (BC) vs. 8.3 mg/d (CC), $p < 0.001$. The mean number of methyl-prednisolone pulses was 3 (BC) vs. 9.3 (CC), $p < 0.001$. HCQ was used by 64% (BC) vs. 100% (CC), $p < 0.001$.

CR rates were 30% (BC) vs. 69% (CC), $p = 0.001$, and 42% (BC) vs. 86% (CC), $p < 0.001$, at 6 and 12 months, respectively. Patients from the CC more frequently achieved CR (adjusted HR 3.8, 95%CI 2.05-7.09). The number of pulses of methyl-prednisolone was associated with CR (adjusted HR 1.09, 95%CI 1.03-1.15). Patients in the CC had a lower risk of GC-related side effects (adjusted HR 0.19, 95%CI 0.04-0.89).

CONCLUSION: The Lupus-Cruces nephritis protocol improves the outcome of LN. Repeated methyl-prednisolone pulses help reduce the dose of oral glucocorticoids and enhance clinical response.

1.- INTRODUCTION

Lupus nephritis (LN) is the most frequent visceral complication of systemic lupus erythematosus (SLE), accounting for an increased morbidity, including end stage renal disease, and mortality (1). Recent consensus treatment guidelines by international panels are congruent, particularly regarding the dose of glucocorticoids (2-5). Induction therapy of class III, IV and V LN is based on high-dose prednisone regimes, with recommended starting doses 0.5 to 1 mg/kg/d, followed by vaguely defined tapering schedules (6). Glucocorticoids are combined with immunosuppressive drugs, mainly cyclophosphamide or mycophenolate. Pulse methyl-prednisolone are usually restricted more severe cases and given only at the beginning of the induction treatment (6).

Despite the important advances in the management of LN, more than 25% of patients fail to achieve complete remission in the long run (1). Notably, the long-term prognosis of lupus patients with renal disease has not changed substantially over the last 10 years (7). Moreover, therapy-related side effects are common, particularly those associated with the use of oral glucocorticoids, a well-known cause of irreversible damage in SLE (8).

Over the last years, some new schemes aiming for using lower doses of prednisone, together with standard therapy (9,10), with combined tacrolimus and mycophenolate mofetil (11) or with rituximab (12) have been proposed. Results from these studies, although still scarce, are encouraging.

The Lupus-Cruces nephritis protocol is based on the combination of repeated pulses of methyl-prednisolone, cyclophosphamide or, less often, mycophenolate, hydroxychloroquine and medium starting doses of prednisone (i.e. always ≤ 30 mg/d) with rapid tapering to 2.5-5 mg/d. A recent study compared the course of 15 patients treated with this protocol with 30 historical controls receiving NIH-like regimes (13). The results showed not only much lower rates of steroid-related toxicity, but also better renal outcomes in patients treated with the reduced dose-prednisone regime.

Encouraging as they are, those data should be corroborated in a bigger sample including a group of contemporary controls. The aim of this study is to compare the clinical course, in terms of renal remission and toxicity, of a larger group of patients with class III, IV and V LN treated with the Lupus-Cruces regime with a cohort of patients of similar characteristics treated at Bordeaux University Hospital according to published current standard of care for severe LN, combining immunosuppressive and glucocorticoid treatments.

2.- PATIENTS AND METHODS

2.1.- Study design and patients.

We conducted a comparison study between two observational LN cohorts whose treatment protocols primarily differed on the patterns of glucocorticoid administration: 1) the Spanish Lupus-Cruces University Hospital Cohort (CC), comprising 29 consecutive patients treated between 2009 and 2015 and 2) the French Bordeaux University Hospital Cohort (BC), with 44 consecutive patients treated between 2008 and 2014.

Eligible patients fulfilled the revised ACR criteria for the classification of SLE (14) and had a class III, IV or V LN as confirmed by renal biopsy (15). The study protocol has been approved by the institutional review boards and ethic committees of Hospital Universitario Cruces and Bordeaux University Hospital. All participants signed an informed consent form before being included in our databases.

2.2.- Treatment protocol: Lupus-Cruces

This protocol has been previously reported (13). For all three classes of LN, induction treatment included three consecutive daily intravenous methyl-prednisolone pulses of 250-500 mg. Oral prednisone was then started at a maximum dose ≤ 30 mg/day, with a rapid tapering to 20, 15 and 10 mg/day every two weeks. This was followed by a tapering of 2.5 mg/day every 4 weeks until a maintenance dose of 2.5-5 mg/day was reached.

As for the immunosuppressive drugs, the agent of choice was as follows:

In class V LN we associated mycophenolate mofetil, at a maximum dose of 1000 mg/12 h.

For both class III and class IV LN, 6 to 9 fortnightly iv pulses of cyclophosphamide 500 mg, according to clinical response, were given. Importantly, 125 mg of iv methylprednisolone was given just before each cyclophosphamide dose. Mycophenolate mofetil was only given as induction therapy in one woman presenting with very low body mass index. After induction was completed, mycophenolate or azathioprine were used.

All patients were prescribed hydroxychloroquine, with no exceptions. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers were used as needed according to blood pressure and the degree of proteinuria. All patients were prescribed calcium and vitamin D.

The protocol-defined visit schedule consisted in regular fortnightly visits during the first 3 months, either fortnightly or monthly visits for the following 3 months and from that moment on, one visit every 1 to 3 months on an individual basis.

2.3.- Treatment protocol: Bordeaux University Hospital

In the BC, patients were treated according current guidelines (2,3,5). Most patients with proliferative forms were treated with the Euro-Lupus Nephritis Trial protocol (16) using low doses of intravenous cyclophosphamide (6 pulses at a fixed dose of 500 mg, given at 2-week intervals) with pulses of methylprednisolone (1 to 3) at the induction therapy. Patients with class V LN were mostly treated with mycophenolate mofetil.

Oral prednisone was generally initiated at a dose of 0.7–1.0 mg/kg/d, and reduced by 2.5–5.0 mg every 2 to 4 weeks until the long-term maintenance dose. Maintenance therapy usually included low-dose glucocorticoid (5 -7.5 mg/d) and azathioprine or mycophenolate mofetil for several years.

The decision of whether to prescribe hydroxychloroquine, antiproteinuric agents and calcium and vitamin D was dependent on an eventual contraindications and the choice of the attending physician.

2.4.- Baseline variables

We compared the following baseline variables of both cohorts: gender, age, ethnicity, class of LN, other SLE manifestations, antiphospholipid syndrome, hypertension (blood pressure $>140/90$ mmHg or need for specific therapy), diabetes mellitus, hyperlipidemia (total cholesterol > 240 or LDL >130 g/l or need for specific therapy), body mass index, baseline proteinuria, as measured by the protein/creatinine (Pr/Cr) ratio in the first morning urine sample (17) or by 24 hours urine collection, estimated glomerular filtration rate (GFR) (ml/min) by the abbreviated MDRD study equation (18), serum albumin levels, C3 titres (mg/dl), anti-DNA, anti-Ro, anti-La, anti-RNP, anti-Sm and antiphospholipid antibodies.

We also compared both groups with regard to the following therapeutic variables: maximum prednisone dose during induction therapy, number of patients with maximum dose of prednisone >30 mg/d, average daily prednisone dose by six months, number of weeks until a 5 mg/day of

prednisone was reached, number of pulses of iv methyl-prednisolone, cumulative methyl-prednisolone dose, cumulative dose of cyclophosphamide at six months, proportion of patients treated with hydroxychloroquine, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and calcium+vitamin D.

2.5.- Outcome measures

The main efficacy outcomes were the proportion of patients in each cohort achieving complete remission (CR) at 6 and 12 months and being on CR, partial remission (PR) or active at the end of follow up. The definition of remission, as stated in the Spanish LN consensus document criteria (4), is as follows:

-CR: defined as a GFR ≥ 60 ml/min/1.73m² (or return to initial GFR or $\pm 15\%$ to the initial value in those with GFR < 60 ml/min/1.73m² at diagnosis) proteinuria ≤ 0.5 g/24 hours, inactive sediment (≤ 5 red blood cells, ≤ 5 leucocytes and absence of hematic casts) and serum albumin > 3 g/dl.

-PR: defined as a decrease in proteinuria below 3.5 g/24 hours in patients with initial nephrotic proteinuria or $> 50\%$ reduction of proteinuria in those with initial values below 3.5 g/24 hours; in both cases, with stabilization ($\pm 25\%$) or improvement in the GFR respect to the initial one.

We also used the urinary Pr/Cr ratio < 0.7 at one year after the diagnosis of LN as a secondary efficacy outcome variable. This cut-off level has been recently identified as a marker for good long-term renal prognosis in European patients with LN, with a positive predictive value of 94% (19).

The toxicity outcome measures included the proportion of patients in each group who developed glucocorticoid-related side effects, defined as metabolic disorders, such as new onset diabetes mellitus, hypercholesterolemia, obesity and/or Cushingoid features, infections, avascular osteonecrosis, osteoporotic fractures and/or cataracts.

2.6.- Statistical analysis

Descriptive data were generated, using percentages, means and standard deviations (SD). Data were compared by Chi-square test, Fisher's exact test, unpaired Student's t-test or Mann-Whitney test, as appropriate.

The outcome of both cohorts was compared by several means: patients achieving complete remission at 6 and 12 months; patients with a urinary Pr/Cr ratio < 0.7 at one year (19); and number of patients on CR or PR at the end of the follow-up. Univariate analysis was performed by Chi-square test. In addition, the reduction in proteinuria at 6 and 12 months in both cohorts was compared by means of Student's t-test. Multivariate analysis was performed using logistic regression with the proportion of patients achieving complete remission at 6 and 12 months as the dependent variables. Time to CR curves were built and compared using log-rank test. Multivariate time dependent analysis was performed by Cox regression. In all regression models, the comparisons between both cohorts were adjusted by age, gender, class of LN, first vs. relapsing LN, anti-DNA, baseline GFR and baseline proteinuria.

Chi-square/Fisher exact test were used to compare the frequency of toxicity attributed to glucocorticoids (metabolic disorders, avascular osteonecrosis, osteoporotic fractures, cataracts, or any of them) in both cohorts. Survival free of toxicity Kaplan-Meier curves were compared by means of log-rank test. Multivariate Cox regression analysis was performed with the following adjusting variables: age, gender, antiphospholipid antibodies and treatment with calcium+vitamin D.

Finally, a pooled analysis of both cohorts was done in order to identify the individual therapeutic predictors of both CR and toxicity. Two Cox regression backwards selection models were fit, one for each outcome. In the CR model, the initial independent variables were: maximum dose of

prednisone, weeks to a dose of prednisone of 5 mg/d, cumulative prednisone dose at 6 months, number of methyl-prednisolone pulses, hydroxychloroquine (yes/no), cyclophosphamide (yes/no), mycophenolate (yes/no) and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (yes/no). In the toxicity model, calcium+vitamin D (yes/no) and treatment with prednisone previous to LN (yes/no) were included in the initial model, whilst hydroxychloroquine was not.

The statistical analysis was done using STATA/MP 14.2 for Mac (StataCorp LP, TX, USA).

3.- RESULTS

3.1.- Demographic and clinical variables

A total of 73 patients were included in the comparative analysis, 44 from BC and 29 from CC. The baseline clinical characteristics of both cohorts are shown on table 1.

Both cohorts were similar for demographic variables, except for a significantly higher age at diagnosis of LN in the CC. There was a higher frequency of previous articular involvement and anti-Sm antibodies among patients from the BC.

Regarding baseline renal features, a lower proportion of patients with class IV LN was seen in the BC (48% vs. 69% in the CC, $p=0.04$). There were no significant differences between both groups in the baseline GFR, urinary protein/creatinine ratio, serum albumin levels, complement levels, proportion of anti-DNA positivity or proportion of hypertensive patients (table 1). The mean (SD) time of follow up after the diagnosis of LN was 43 (21) months in the BC and 46 (26) in the CC, $p=0.4$.

3.2.- Treatment

The mean (SD) maximum dose of oral prednisone at induction was 42.5 mg/day (22) in the BC vs. 21 (7) in the CC ($p<0.001$); no patients in the CC received doses >30 mg/d, vs. 75% of patients in the BC (range 30-100 mg/d). As for the weeks to reduction of prednisone to 5 mg/day, the mean (SD) was 22 (6.4) in the BC vs. 12.4 (4.4) in the CC ($p<0.001$). Within 6 months, the calculated mean (SD) prednisone dose was 21 mg/d (11.7) in the BC vs. 8.3 mg/d (1.6) in the CC ($p<0.001$).

In the BC, 75% of patients received pulses of methyl-prednisone, vs. 100% in the CC ($p=0.002$). The mean (SD) number of iv methylprednisolone pulses per patient was 3 (0.5) in the BC vs. 9.3 (3.3) in the CC ($p<0.001$). However, the difference in the cumulative methylprednisolone dose was non significant between both groups (1.9 vs. 1.7 gr, respectively, $p=0.3$), reflecting the use of lower doses of methylprednisolone per pulse in the CC (13).

The use of cyclophosphamide for induction treatment was significantly less frequent in the BC: 57% vs. 79%. $p=0.048$. However, the mean (SD) cumulative dose of cyclophosphamide in patients treated with this drug was similar in both cohorts: 3.3 (0.9) vs. 3.5 gr (1.2), respectively, $p=0.48$. There were no differences regarding the use of mycophenolate (82% vs. 79%, $p=0.8$).

The use of hydroxychloroquine was 100% in the CC vs. 64% in the BC ($p<0.001$) because of retinal contra-indication in half patients. Adjuvant therapy with calcium+ vitamin D was administered to 70.5% patients in the BC vs. 97% patients in the CC ($p=0.006$). Angiotensin converting enzyme inhibitors/angiotensin receptor blockers were used in 73% and 76% of patients in the BC and CC, respectively ($p=0.7$).

Within the total follow-up, 4 patients in the BC were treated with rituximab for a relapse, vs. 1 in the CC, who received this therapy for an episode of alveolar hemorrhage after the second pulse of cyclophosphamide.

3.3.- Clinical response at 6 months (table 2)

At 6 months, 30% of patients in the BC achieved complete remission vs. 69% in the CC ($p=0.001$). Patients in the CC were significantly more likely to achieve CR at 6 months (adjusted OR 9.42, 95%CI 2.5-35.7). Baseline proteinuria was the only additional significant predictor of a worse outcome (adjusted OR 0.58, 95%CI 0.4-0.8).

Proteinuria was significantly reduced in both cohorts, from a mean 3.04 gr/d to 1.41 gr/d ($p<0.001$) in the BC, and from 3.44 to 0.52 gr/d in the CC ($p<0.001$); thus, the reduction in proteinuria was about two-fold among patients from the CC (2.9 vs. 1.6, $p=0.05$).

3.4.- Clinical response at 12 months (table 2)

At 12 months, 42% patients achieved CR in the BC (one patient did not complete one year of follow-up) vs. 86% in the CC ($p<0.001$). Patients in the CC were more likely to achieve CR at 12 months (adjusted OR 9.6, 95%CI 2.2-41.4). A higher baseline proteinuria also decreased the likelihood of CR at 12 months (adjusted OR 0.69, 95%CI 0.5-0.9).

The proportion of patients with proteinuria <0.7 at 12 months was 58% in the BC vs. 90% in the CC ($p=0.013$). The reduction in proteinuria at 12 months was also higher in the CC: 3.4 vs. 1.9, $p=0.06$.

3.5.- End of follow-up

At the end of the follow up, 31 patients (70.5%) from the BC were in CR, 4 (9%) were in PR and 9 (20.5%) were not in remission; all 29 patients from the CC were in CR at the end of the follow-up ($p=0.002$). The frequency of relapses was not significantly different between both groups: 14% in the BC vs. 7% in the CC, $p=0.3$. Only one patient in the BC and none in the CC eventually required substitutive renal therapy. No patients in any cohorts received kidney transplantation.

3.6.- Survival analysis.

As shown on figure 1A, patients from the CC achieved CR earlier and more frequently, with a 100% final CR rate ($p<0.001$).

In the Cox regression analysis, patients from CC were almost 4 times more likely to achieve CR during the follow up (adjusted HR 3.8, 95%CI 2.05-7.09). In the final model, only the degree of proteinuria at diagnosis of LN (HR 0.84, 95%CI 0.74-0.94) and being in the CC (HR 3.19, 95%CI 1.9-5.3) were independently associated with a lower and higher likelihood, respectively, of achieving CR (table 3).

In the pooled analysis (table 4), the only treatment variable independently associated with CR was the number of pulses of iv methyl-prednisolone (HR 1.09, 95%CI 1.03-1.15).

3.7.- Glucocorticoid related toxicity

Global GC-associated toxicity was significantly more frequent among patients in the BC (34% vs. 7%, $p=0.007$). The GC-toxicity survival curves (fig 1B) show that patients in CC were less likely to suffer GC-related side effects in a time-dependent way ($p=0.01$). Cox regression confirmed the independent lower risk of developing GC-related patients in the CC (adjusted HR 0.19, 95%CI 0.04-0.89). No other individual predictor was identified.

Regarding each individual adverse effect, we found a statistically significant difference between the two cohorts regarding the global metabolic toxicity (BC 34.09% vs. CC 6.9%, $p=0.007$) dyslipidemia (BC 18.18% vs. CC 0%, $p=0.015$) and moon-face (11% vs. 0%, $p=0.06$). The remaining complications analysed (striae, infections, vertebral fractures, avascular necrosis and cataracts) were infrequent overall and did not differ significantly between both groups.

Analysing the therapeutic variables associated with GC toxicity, the maximum dose of prednisone received was the strongest predictor (adjusted HR 1.03, 95%CI 1.01-1.05); on the other hand, the number of pulses of methyl-prednisolone were inversely related with GC-related side effects (adjusted HR 0.82, 95%CI 0.68-1.01) (table 5).

4.- DISCUSSION

The Lupus-Cruces nephritis protocol has been used for more than 8 years. Oral prednisone has been consistently given at doses below 30 mg/d, with very rapid tapering to 5 mg/d within, at most, 14 weeks; on the other hand, pulses of methyl-prednisolone have not been limited to the first three days of induction, but given every two weeks to potentiate the effects of iv. cyclophosphamide. As adjuvant therapy, HCQ has been used in all patients with LN.

This study reinforces our previous results compared with historical controls (13). The number of patients treated with the Lupus-Cruces nephritis protocol has doubled, with all suffering from class III, IV and V LN (69% with class IV). The control group was contemporary, external to our centre, coming from a University Hospital and treated according to current guidelines (2,3,5); actually, the remission rates seen in the BC were quite the expected according to published data (11,16,20).

We used a crude main endpoint such as CR according to international consensus guidelines (6). We added an analysis using a proteinuria level <0.7 at one year, a strong predictor of good long-term renal outcome in the MAINTAIN trial cohort (19). Whatever the endpoint used, the results in the CC were statistically superior to those in the BC. Of note, the proportion of patients achieving the 0.7 proteinuria threshold at one year was 90% in the CC, vs. 59% in the BC and 65% in the MAINTAIN trial (19). The occurrence of glucocorticoid-related toxicity in the CC was almost exceptional.

The pooled analysis identified an independent association between the number of methyl-prednisolone pulses received and the likelihood of achieving remission. In fact, giving one extra methyl-prednisolone pulse every two weeks, just before each dose of cyclophosphamide, is the main differential characteristic of our therapeutic scheme.

It is well known that glucocorticoids exert strong anti-inflammatory and immunosuppressive effects through genomic and non-genomic mechanisms (21). Most of the toxic effects are related to the genomic way (21). In order to get fast anti-inflammatory and immunosuppressive effects it is necessary to activate the non-genomic way, which is restricted to very high doses of glucocorticoids (prednisone-equivalent of >100 mg per day) or pulse therapy (≥ 250 mg/d) (22). Methyl-prednisolone pulses can also help rapidly reduce the dose of oral prednisone (23). Such reduction obviously results in a dramatic decrease of side effects; however, it could also help achieve renal remission by a different way.

It is known that prolonged oral glucocorticoid therapy at high doses can promote proteinuria through increasing weight gain (24). In addition, data from both animal models (25) and human clinical studies (26-30) show a direct effect of glucocorticoids on glomerular permeability and, thus, on the degree of proteinuria. Notably, patients with nephrotic syndrome due to idiopathic membranous glomerulonephritis or minimal change disease receiving alternate-day glucocorticoid regimes, had significantly higher levels of proteinuria on the day taking glucocorticoids (26,27,30). Prolonged therapy with high-dose prednisone could thus increase renal protein leak, leading to the assumption of lack of response. The patient could then enter in a vicious circle with further increasing the dose of steroids, which eventually ends up in an incomplete response and in long term renal damage accrual. It is our view that, in at least a proportion of patients who do not achieve CR, high-dose oral glucocorticoids could actually contribute to the unfavourable clinical course. The Lupus-Cruces nephritis regime can improve the clinical response of patients thanks to a more rational use of glucocorticoids: more methyl-prednisolone pulses, less oral prednisone. A similar regime has also proved effective and safe in patients with other forms of severe SLE (31).

The main limitation of this study is the observational design. It can be argued that treatments were not randomly assigned, that a theoretical number of confounders may be biasing the results and that the number of patients included was relatively low. However, numbers were big enough to show marked differences in treatment regimes, renal outcomes and toxicity between both cohorts. Patients in our study were representative of European patients with LN and well illustrated real clinical practise in Europe; in fact, the French cohort was very similar in terms of therapy and response rates to the Euro lupus Nephritis Trial cohort (16). The variables used for renal outcome were simple, widely used and well validated, including the recently identified urinary Pr/Cr ratio <0.7 as a surrogate marker for good long-term renal prognosis (19). The outcome analyses were controlled by the main potential predictors of response, including baseline glomerular filtration rate, baseline proteinuria, class of LN, first vs. relapsing LN, anti-DNA antibodies, age and gender.

Therefore, we believe that, despite the intrinsic limitations of this kind of study, our data support the use of regimes including repeated methyl-prednisolone pulses and medium-low doses of oral prednisone to treat patients with LN.

TAKE-HOME MESSAGES

- Lupus nephritis regimes based on high-dose-prednisone fail to achieve complete remission in 25% of patients.
- The Lupus-Cruces nephritis protocol improves renal outcome and decreases toxicity in severe lupus nephritis.
- A more restrictive use of oral prednisone can be achieved by giving fortnightly methylprednisolone pulses.

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COMPETING INTERESTS

The authors declare that they have no competing interest.

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Table 1: Baseline clinical characteristics and therapy for lupus nephritis.

Baseline clinical variables			
	Bordeaux	Cruces	p
Gender (female/male)	36/8	22/7	0.5
Age at diagnosis of LN (years) mean (SD)	35 (12.4)	43 (12.2)	0.014
Ethnicity			
White	33 (77%)	25 (86%)	0.5
Black	1 (2%)	1 (3.5%)	
Asian	2 (5%)	0 (0%)	
North African	2 (5%)	2 (7%)	
Latin-American	5 (11%)	1 (3.5%)	
Class LN			
Class III	20 (45%)	5 (17%)	0.04
Class IV	21 (48%)	20 (69%)	
Class V	3 (7%)	4 (14%)	
First episode of LN	21 (48%)	19 (65%)	0.13
SLE manifestations			
Skin	31 (70%)	15 (52%)	0.1
Articular	40 (90%)	18 (62%)	0.003
Hematological	19 (43%)	12 (41%)	0.8
Serositis	9 (20%)	9 (31%)	0.3
Antiphospholipid syndrome	4 (9%)	1 (3%)	0.3
Hypertension (>140/90)	14 (32%)	6 (21%)	0.3
Diabetes mellitus	0 (0%)	1 (3.5%)	0.4
Total cholesterol> 240 or LDL>130 (g/l)	9 (35%)	7 (24%)	0.4
Body mass index >30	2 (5%)	2 (7%)	0.4

	Bordeaux	Cruces	p
<i>antiDNA positivity</i>	42 (95%)	26 (90%)	0.3
<i>Anti-Ro positivity</i>	20 (45%)	12 (41%)	0.7
<i>Anti-RNP positivity</i>	17 (39%)	5 (17%)	0.05
<i>Anti-Sm positivity</i>	15 (34%)	3 (10%)	0.021
<i>Anticardiolipin >40 x2</i>	0 (0%)	2 (7%)	0.07
<i>Positive Lupus anticoagulant x2</i>	3 (7%)	5 (17%)	0.16
<i>C3 titers (mg/dL) mean (SD)</i>	60.5 (22.35)	62.7 (30.5)	0.7
<i>Proteinuria (g/24h) mean (SD)</i>	3.0 (2.4)	3.44 (3.9)	0.5
<i>Albumin level at diagnosis g/dL mean (SD)</i>	2.8 (0.74)	3.14 (0.6)	0.09
<i>GFR (ml/min/1.73m2) mean (SD)</i>	83.2 (52.05)	77.8 (35.4)	0.6

Treatment for lupus nephritis			
	Bordeaux	Cruces	p
Maximum dose of prednisone (mg/d) mean (SD)	42.5 (22)	21 (7)	<0.001
Patients with maximum dose of prednisone >30 mg/d	33 (75%)	0	<0.001
Weeks to prednisone at 5 mg/day mean (SD)	22 (6.4)	12.4 (4.4)	<0.001
Average prednisone dose within 6 months (mg/d) mean (SD)	21 (11.7)	8.3 (1.6)	<0.001
Patients with methylprednisolone pulses	33 (75%)	29 (100%)	0.002
N methylprednisolone pulses per patient mean (SD)	3 (0.5)	9.3 (3.3)	<0.001
Cumulative methylprednisolone dose (gr) mean (SD)	1.9 (0.9)	1.7 (0.7)	0.3
Patients on cyclophosphamide	25 (57%)	23 (79%)	0.048
Cumulative dose of cyclophosphamide (gr) mean (SD)	3.3 (0.9)	3.5 (1.2)	0.48
Patients on mycophenolate	36 (82%)	23 (79%)	0.8
Patients on hydroxychloroquine	28 (64%)	29 (100%)	<0.001
Antiproteinuric agents	32 (73%)	22 (76%)	0.7
Calcium + vitamin D	31 (70.5%)	28 (97%)	0.006

LN: lupus nephritis

SLE: systemic lupus erythematosus

GFR: glomerular filtration rate

Table 2: Clinical response at 6 months, 12 months and end of follow-up.

	Bordeaux (n=44)	Cruces (n=29)	p
<i>CR at 6 months</i>	13 (30%)	20 (69%)	0.001
<i>CR at 12 months</i>	18* (42%)	25 (86%)	<0.001
<i>CR at the end of follow-up</i>	31 (70.5%)	29 (100%)	0.002
<i>Pr/Cr <0.7 at 12 months</i>	25* (58%)	26 (90%)	0.013
<i>Proteinuria reduction at 6 months (gr) mean (SD)</i>	1.6	2.9	0.05
<i>Proteinuria reduction at 12 months (gr) mean (SD)</i>	1.9	3.4	0.06

CR: Complete response

Pr/Cr: urinary protein/creatinine ratio

* One patient did not complete one year of follow-up

Table 3. Time-dependent predictors of complete response

	Initial model HR (95% CI)	Final model HR (95% CI)
<i>Cruces Cohor (vs. Bordeaux Cohort)</i>	3.8 (2.05-7.09)	3.19 (1.9-5.3)
<i>Age at diagnosis of lupus nephritis</i>	1.007 (0.98-1.02)	
<i>Male gender</i>	0.93 (0.46-1.85)	
<i>Baseline anti-DNA antibodies</i>	1.8 (0.7-4.6)	
<i>Lupus nephritis class</i>	0.78 (0.5-1.19)	
<i>First episode of lupus nephritis</i>	1.28 (0.71-2.3)	
<i>Baseline proteinuria</i>	0.84 (0.75-0.95)	0.84 (0.74-0.94)
<i>Baseline GFR</i>	0.99 (0.99-1.01)	

GFR: glomerular filtration rate

HR: hazard ratio

CI: confidence interval

Table 4: Pooled analysis of time-dependent therapeutic predictors of complete response

	Initial model HR (95% CI)	Final model HR (95% CI)
<i>Maximum dose of prednisone (mg/d)</i>	1.02 (0.99-1.05)	
<i>Time to prednisone 5 mg/d (weeks)</i>	0.98 (0.93-1.04)	
<i>Mean prednisone dose at 6 months (mg/d)</i>	0.95 (0.98-1.02)	
<i>N of methyl-prednisolone pulses</i>	1.07 (1.00-1.15)	1.09 (1.03-1.15)
<i>Hydroxychloroquine</i>	1.36 (0.61-3.01)	
<i>Cyclophosphamide</i>	0.58 (0.3-1.01)	
<i>Mycophenolate</i>	0.64 (0.32-1.31)	
<i>Antiproteinuric drugs</i>	0.43 (0.22-0.82)	

HR: hazard ratio

CI: confidence interval

Table 5: Pooled analysis of time-dependent therapeutic predictors of glucocorticoid-related toxicity

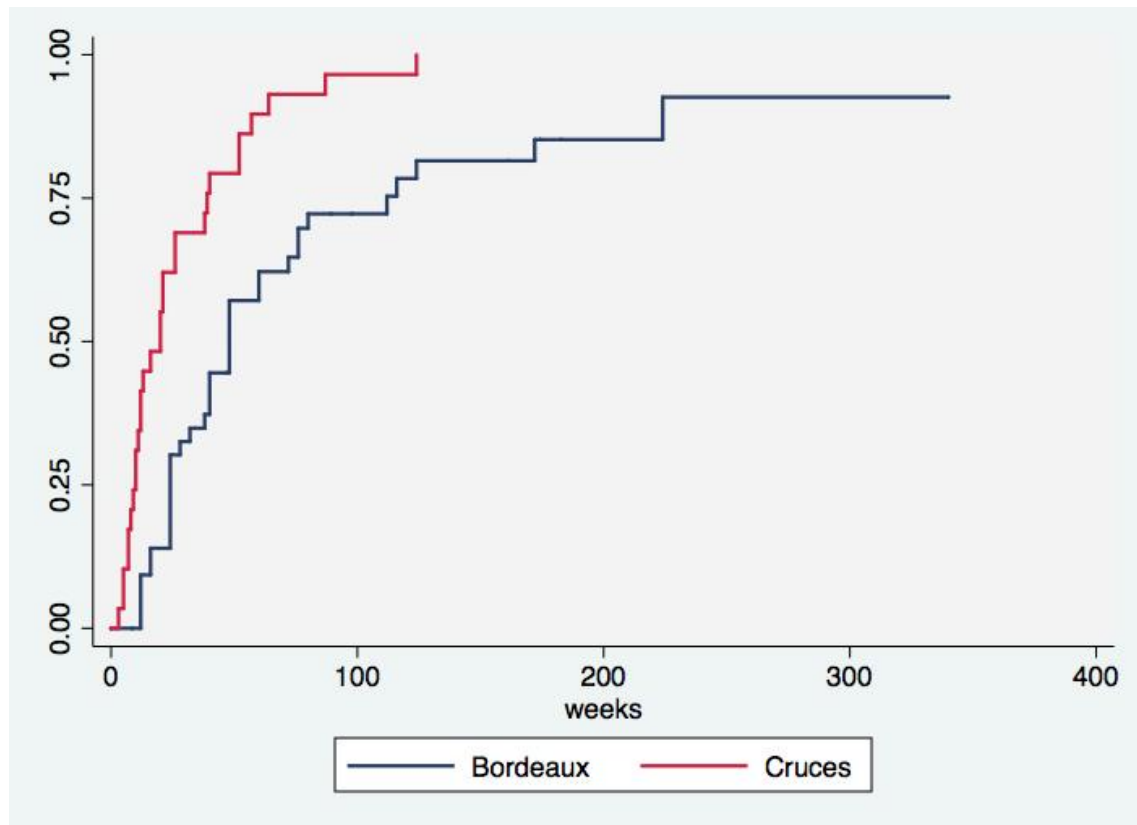
	Initial model HR (95% CI)	Final model HR (95% CI)
<i>Maximum dose of prednisone (mg/d)</i>	1.09 (1.01-1.17)	1.03 (1.01-1.05)
<i>Time to prednisone 5 mg/d (weeks)</i>	0.95 (0.82-1.09)	
<i>Mean prednisone dose at 6 months (mg/d)</i>	0.65 (0.37-1.13)	
<i>N of methyl-prednisolone pulses</i>	0.71 (0.53-0.94)	0.82 (0.68-1.01)
<i>Calcium + Vitamin D</i>	2.91 (0.59-14.21)	
<i>Cyclophosphamide</i>	1.10 (0.75-1.62)	
<i>Mycophenolate</i>	1.68 (0.30-9.48)	
<i>Antiproteinuric drugs</i>	0.52 (0.14-1.96)	

HR: hazard ratio

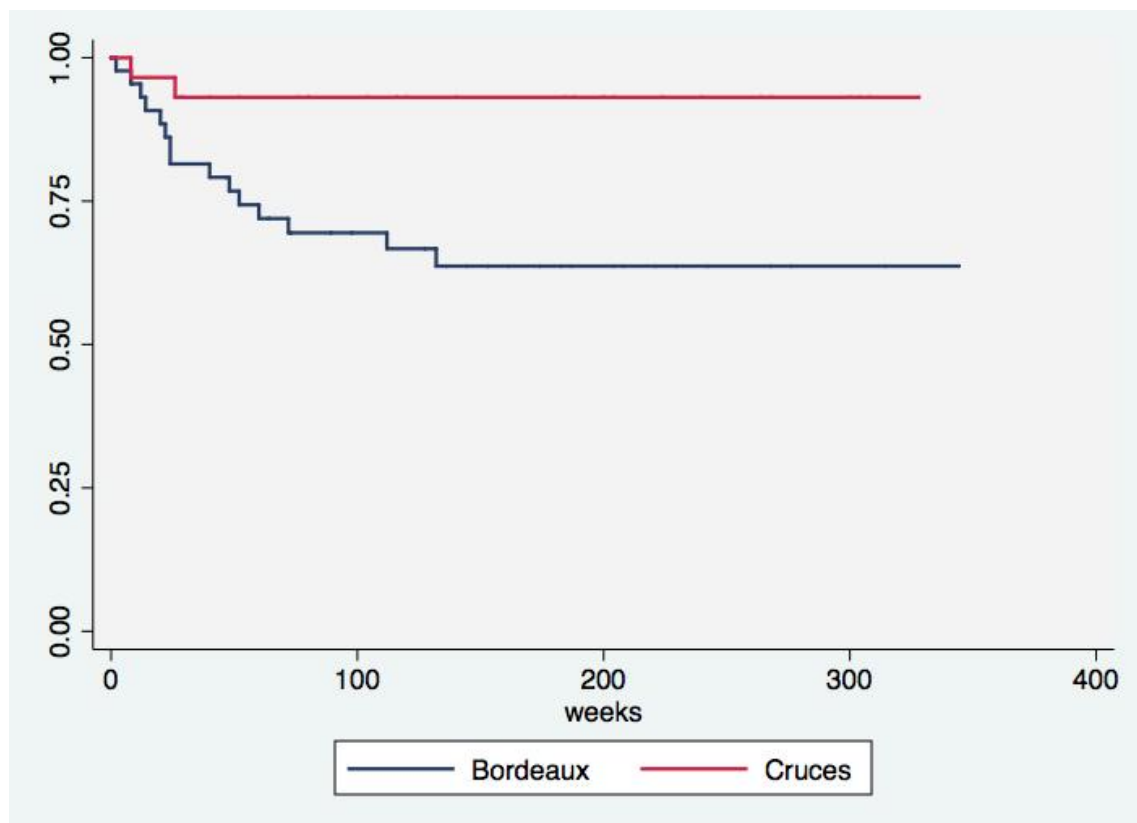
CI: confidence interval

Figure: Complete remission (A) and Glucocorticoid-related toxicity (B) curves.

A)



B)



Conclusion

Lupus nephritis is a common and severe manifestation of SLE and an important cause of both acute kidney injury and ESRD.

The GCs therapy still remains the cornerstone of the treatment and most effective therapy in managing SLE despite advances in other immunosuppressive drugs, therapeutic protocols and development of new drugs. GCs rapidly control disease activity in mild as well as in severe disease, although these effects depend on the doses and could vary among patients. Despite their important clinical efficacy, GCs produce several adverse reactions, most being time and dose dependent, limiting their clinical usefulness.

The majority of SLE patients are treated with GCs; some of them continue this treatment indefinitely as maintenance therapy.

Recent guidelines confirm the lack of randomised trial evidence to support any particular regimen of GCs used in either the induction or maintenance of lupus nephritis treatment. The scientific societies recommend judicious use of these agents, taking into consideration the potential harms associated with these drugs.

Our study highlighted the fact that GCs should not be continued indefinitely, regimens could be shorter with lower doses of oral GCs and the use of methylprednisolone boli in acute situation could be helpful in order to control disease activity with the goal of adequately control inflammatory symptoms while minimising steroid exposure in order to reduce deleterious adverse effects.

Further studies are needed to speculate the optimal dose, dosage frequency, the route, the duration of GCs and how this treatment should be discontinued in patients with SLE in induction and maintenance therapies to reach the best response and prevent side effects.

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LE SERMENT D'HIPPOCRATE

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

RÉSUMÉ

Evaluer la dose optimale de glucocorticoïdes pour traiter la néphrite lupique : Une collaboration entre Bordeaux et Bilbao.

OBJECTIF : Comparer l'évolution clinique des patients atteints de néphrite lupique (NL) de classe III, IV et V traités à l'Hospital Universitario Cruces (CC) et à l'hôpital universitaire de Bordeaux (BC).

METHODE : Le protocole Lupus-Cruces pour la néphrite lupique combine des boli de 125 mg de méthylprednisolone associés à chaque bolus bimensuel de cyclophosphamide et à la prise de prednisone ≤ 30 mg/jour avec une décroissance sur 12 à 14 semaines jusqu'à 2.5-5 mg/jour. BC a suivi les lignes directrices internationales sur les néphrites lupiques, combinant une dose élevée de prednisone soit au mycophénolate mofetil, soit au cyclophosphamide, suivi d'un traitement d'entretien avec une faible dose de prednisone et des médicaments immunosuppresseurs. Les critères de jugements principaux étaient la rémission rénale complète (RC) et la toxicité des glucocorticoïdes (GCs).

RESULTATS : 44 patients de BC et 29 de CC ont été inclus. La dose maximale moyenne de prednisone était de 42.5 (BC) contre 21 mg/jour (CC), $p < 0.001$. La dose moyenne de prednisone à 6 mois était de 21 (BC) contre 8.3 mg/jour (CC), $p < 0.001$. Le nombre moyen de boli de méthylprednisolone était de 3 (BC) contre 9.3 (CC), $p < 0.001$. L'hydroxychloroquine a été utilisée par 64% (BC) contre 100% (CC), $p < 0.001$.

Les taux de RC étaient de 30% (BC) contre 69% (CC), $p = 0.001$ et 42% (BC) contre 86% (CC), $p < 0.001$, respectivement à 6 et 12 mois. Les patients de CC ont plus fréquemment atteint une RC (HR ajusté 3.8, IC 95% CI 2.05-7.09). Le nombre de boli de méthylprednisolone était associé à la RC (HR ajusté 1.09, IC 95% 1.03-1.15). Les patients dans le CC ont un risque plus faible d'effets secondaires liés aux GCs (HR 0.19 ajusté, IC 95% 0.04-0.89).

CONCLUSION : Le protocole Lupus-Cruces concernant les néphrites améliore l'issue de la NL. Les boli répétés de méthylprednisolone contribuent à réduire la dose de GCs par voie orale et à améliorer la réponse clinique.

Mots clés : Lupus érythémateux systémique, Néphrite lupique, Glucocorticoïdes, Methylprednisolone, Prednisone, Effets indésirables

ABSTRACT

Assess the optimal dose of glucocorticoids to treat lupus nephritis: collaboration between Bordeaux and Bilbao.

OBJECTIVE: To compare the clinical course of patients with class III, IV and V lupus nephritis (LN) treated in Hospital Universitario Cruces (CC) and in Bordeaux University Hospital (BC).

METHODS: The Lupus-Cruces nephritis protocol combines pulses of 125 mg of methyl-prednisolone with each fortnightly pulse of cyclophosphamide and prednisone ≤ 30 mg/day with tapering over 12-14 weeks until 2.5-5 mg/day. The BC followed international lupus nephritis guidelines, combining high-dose prednisone and either mycophenolate mofetil or cyclophosphamide, followed by maintenance therapy with low dose prednisone and immunosuppressive drugs. The main outcomes were complete renal remission (CR) and glucocorticoid toxicity.

RESULTS: 44 patients from BC and 29 CC were included. The mean maximum prednisone dose was 42.5 (BC) vs. 21 mg/day (CC), $p < 0.001$. The average 6-month prednisone dose was 21 (BC) vs. 8.3 mg/d (CC), $p < 0.001$. The mean number of methyl-prednisolone pulses was 3 (BC) vs. 9.3 (CC), $p < 0.001$. HCQ was used by 64% (BC) vs. 100% (CC), $p < 0.001$.

CR rates were 30% (BC) vs. 69% (CC), $p = 0.001$, and 42% (BC) vs. 86% (CC), $p < 0.001$, at 6 and 12 months, respectively. Patients from the CC more frequently achieved CR (adjusted HR 3.8, 95%CI 2.05-7.09). The number of pulses of methyl-prednisolone was associated with CR (adjusted HR 1.09, 95%CI 1.03-1.15). Patients in the CC had a lower risk of GC-related side effects (adjusted HR 0.19, 95%CI 0.04-0.89).

CONCLUSION: The Lupus-Cruces nephritis protocol improves the outcome of LN. Repeated methyl-prednisolone pulses help reduce the dose of oral glucocorticoids and enhance clinical response.

Key words: Systemic lupus erythematosus, Lupus nephritis, Glucocorticoids, Methyl-prednisolone, Prednisone, Side effects