Development and Implementation of a Pilot Registry for Monitoring the Efficacy and Safety of Novel Therapies in Patients with Systemic Lupus Erythematosus

Christina Adamichou, Irini Flouri, Antonios Fanouriakis, Myrto Nikoloudaki, Dionysios Nikolopoulos, Argyro Repa, Kyriaki Boki, Katerina Chatzidionysiou, Alexandros Garyfallos, Dimitrios Boumpas, Prodromos Sidiropoulos, George Bertsias

Mediterr J Rheumatol 2020;31(1):87-91
Development and Implementation of a Pilot Registry for Monitoring the Efficacy and Safety of Novel Therapies in Patients with Systemic Lupus Erythematosus

Christina Adamichou1, Irini Flouri1, Antonios Fanouriakis2, Myrto Nikoloudaki1, Dionysios Nikolopoulos3, Argyro Repo1, Kyriaki Boki4, Katerina Chatzidionysiou5,6, Alexandros Garyfallos7, Dimitrios Boumpas3, Prodromos Sidiropoulos1, George Bertsias1

1Rheumatology and Clinical Immunology, University of Crete Medical School and University Hospital of Heraklion, Heraklion, Greece, 2Rheumatology Clinic, General Hospital of Athens “Asklepieion Voula”, Athens, Greece, 3Rheumatology Clinic, 4th Department of Internal Medicine, National and Kapodistrian University of Athens, “Attikon” University Hospital, Athens, Greece, 4Rheumatology Clinic, “Sismanoglio” General Hospital, Athens, Greece, 5First Department of Propaedeutic Internal Medicine, National and Kapodistrian University of Athens, “Laiko” General Hospital, Athens, Greece, 6Department of Medicine, Solna, Rheumatology Unit, Karolinska University Hospital and Institutet, Stockholm, Sweden, 74th Department of Internal Medicine, Hippokration General Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

ABSTRACT

The therapeutic armamentarium in Systemic Lupus Erythematosus (SLE) is expanding with the introduction of novel biologic and small-molecule agents. Complementary to randomized controlled trials, registry-based studies are advantageous due to the inclusion of a wider range of patients from daily practice and the potential for long-term monitoring of the efficacy and safety of therapies. Moreover, data from registries can be used to identify disease phenotypes that best respond to biologic agents, and to correlate clinical response with parameters such as co-administered therapies and comorbidities. In this project, we will use the configuration of the Hellenic Registry of Biologic Therapies for inflammatory arthritides in order to design a dedicated SLE module with variables pertaining to global and organ-specific disease activity, severity, flares, organ damage/outcome, comorbidities and adverse events. The second stage will involve the pilot implementation

BACKGROUND AND STUDY RATIONALE

Systemic lupus erythematosus (SLE) encompasses a wide range of clinical and immunological manifestations, which makes monitoring of patients and assessment of their response to therapy a challenging task.1 For many years, treatment of SLE was based primarily on the administration of corticosteroids and non-specific immunomodulators/suppressors or cytotoxic agents. Although these agents are generally efficacious in controlling the disease, still, a considerable proportion of patients fails to achieve long-standing remission.2 Importantly, conventional drugs, particularly corticosteroids, are associated with excessive toxicity risks, accrual of comorbidities and irreversible end-organ damage.3 Scientific advancements in our understanding of the immunopathogenesis of SLE, coupled with better-designed clinical studies,4 have led to the expansion of the therapeutic armamentarium due to repositioning of drugs administered in other medical conditions (eg, mycophenolate5) and the increasing use of approved (e.g. belimumab6) and non-approved (eg, rituximab7) biologic agents. Based on the findings of recently performed controlled trials,8-14 a number of innovative therapies in SLE, including monoclonal antibodies (eg, anifrolumab, ustekinumab, obinutuzumab) and small molecules (eg, Janus kinase inhibitors), are expected to be introduced in the near future.
Post-marketing analysis of the efficacy and safety of new drugs is important in defining their application in routine clinical practice. In addition to the results from randomized clinical trials (RCTs), a significant amount of information can be derived from patient registries that systematically assess the effects of treatments under “real-life” conditions. Registries are also advantageous because they allow the inclusion of a wide spectrum of patients without the stringent exclusion criteria of RCTs (eg, patients with co-morbidities or less frequent disease manifestations), and monitoring for long-term drug efficacy and safety (including rare adverse events).15,16 In the case of SLE, which is a multifaceted, systemic autoimmune disease, data from organized patient registries may be particularly useful to approach clinically-relevant issues that cannot be easily addressed through clinical trials. These may include, for instance, the definition of disease endo-phenotypes that respond better to individual treatments, and the association between drug efficacy/safety with various disease parameters (co-administered treatments, comorbidities, etc.). Furthermore, collected data may help to obtain unique insights into the mechanisms of action of novel therapies. The value of establishing registries of patients receiving biological agents has been illustrated in inflammatory arthritides (rheumatoid arthritis, spondyloarthritis). Thus, analysis of registry-derived data has shed light on topics such as the identification of clinical factors that are predictive of treatment response, the safety of biologics in terms of the risk for latent infections and malignancies, the use of sequential therapies (‘switches’), the main causes of drug discontinuations and other.17-20 Likewise, large SLE registries, such as the Johns Hopkins Lupus Cohort, have provided significant knowledge with regards to the dose-dependent corticosteroid toxicity and the role of hydroxychloroquine in prevention of disease flare-ups.1,3 Another example is the British Isles Lupus Assessment Group (BILAG) Biologics Register of SLE patients, which has described the main features of patients who are candidates for biological treatment and has investigated the short-term efficacy and safety associated with the use of rituximab.7 To date, there is no structured platform for registering SLE patients in Greece under biologic therapies, and, accordingly, there is paucity of data on the indications, long-term efficacy and safety of these agents in real-life clinical settings. In this study, we seek to establish and implement a pilot system for the electronic registration and monitoring of patients with SLE who are treated with existing biologic but also, future novel therapeutics agents.

AIMS OF THE STUDY
The aim of the present study is to establish and run a pilot study of an electronic registry for monitoring SLE patients who are treated with novel/biologic therapies. The study has multicentric, prospective design with two implementation stages.

METHODS
Study design
This is a prospective study that will be performed at the Rheumatology Clinic, University of Crete Medical School and University Hospital of Heraklion (involved at stages I and II of the protocol) in collaboration with the Rheumatology Units/Clinics of the “Attikon” University Hospital, “Laiko” General Hospital, General Hospital of Asklepieion Voula, Hippokration University Hospital of Thessaloniki, and “Sismanogleio” General Hospital (involved at stage II of the protocol). The study has been approved by the Ethics Committees of the participating centers. The first stage (0–6 months) of the protocol includes the design of a specialized electronic platform (registry) for patients with SLE. The development of the registry will be based on the configuration and software of the existing registry of patients with chronic inflammatory arthritides who are treated with biologic agents (University of Crete, Medical School),17 following amendments to capture at each visit: the dosage of main and secondary treatments,
Therapies for patients with inflammatory arthritides.

and configuration of the Hellenic Registry of Biologic

The SLE registry module will be based on the structure and ability to export selected data for further analysis. In line with the General Data Protection Regulation (GDPR) we also plan to update the long-term efficacy and safety data of a previously published cohort of patients. We will assess the effectiveness (both globally and across individual organs/domains), attainment of low disease activity and remission states, the co-administration of glucocorticoids and other treatments, major events (comorbidities) and adverse events (outlined below).

Design of the electronic registry

An online software is under development at the Rheumatology Clinic, University of Crete Medical School, in collaboration with the Centre for eHealth Applications and Services (CeHA) at the Institute of Computer Science, Foundation for Research and Technology – Hellas (ICS-FORTH) (http://web-new.ics.forth.gr/ceha/). This is a web-based platform with secure connection, anonymised entry of patient data, encrypted data storage in line with the General Data Protection Regulation (GDPR) and ability to export selected data for further analysis. The SLE registry module will be based on the structure and configuration of the Hellenic Registry of Biologic Therapies for patients with inflammatory arthritides.\(^{17}\)

Registry variables

From each patient, the following variables will be collected at inclusion visit (initiation of treatment) and/or at regular (6-month) follow-up intervals:

- Demographics (gender, nationality, date of birth)
- Date of diagnosis
- SLE classification criteria (ACR 1997,\(^{21}\) SLICC 2012,\(^{22}\) EULAR/ACR 2019\(^{23}\))
- Disease stratification (mild, moderate, severe) based on BILAG-defined organ activity,\(^{25,26}\) administration of corticosteroids and use of potent immunosuppressive/cytotoxic or biologic treatments
- Disease activity pattern (relapsing-remitting, chronic active)
- Global activity indices (SLEDAI-2000,\(^{27}\) Physician Global Assessment [PhGA]\(^{30}\))
- Organ-specific activity indices (CLASI index for cutaneous lupus,\(^{29}\) tender and swollen joint counts, proteinuria, Likert scale for neurological deficits)
- Disease flares (SELENA-SLEDAI Index\(^{28}\))
- Definitions of Lupus Low Disease Activity State (LLDAS)\(^{30}\) and remission\(^{31}\)
-Irreversible organ damage (SLICC/ACR Damage Index\(^{25}\))
- Functional status (Health assessment questionnaire disability index [HAQ-DI]\(^{33}\))
- Comorbidities (Rheumatic Disease Comorbidity Index [RDCI]\(^{34}\))
- Treatments (previous, ongoing): detailed record of medications (main treatment, concomitant disease treatments) and administered forms/dosage
- Adverse reactions and events (MedDRA recording system; https://www.meddra.org/faq/meddra-general), treatment discontinuations

Data entry and collection

Each participating centre will be granted access to the electronic platform (registry) with unique credentials in order to enter their own patient data. As this is a pilot implementation of the registry, we aim to enrol a total of 60 SLE patients under treatment with belimumab, which will allow to obtain statistically robust results.

Statistical analysis

A single export of merged patient data from all centres will be obtained for statistical analysis (months 31-36). Descriptive results on demographics, proportion of patients with partial or complete clinical response, attainment of LLDAS and remission/flares will be calculated. Efficacy will be correlated with baseline clinical and demographic characteristics. Safety will be assessed according to occurrence of major events. Treatment survival and reasons for discontinuation will also be evaluated.

ANTICIPATED RESULTS AND PROJECT SIGNIFICANCE

Registries of patients with chronic rheumatic diseases receiving biological therapies have provided significant insights regarding their long-term efficacy and safety in “real-life” clinical practice. In recent years, biological agents such as belimumab and rituximab have been introduced in the treatment of SLE, and based on the results from ongoing clinical trials, it is likely that additional innovative therapies may be added in the near future. The importance of this project lies in the development and pilot use of a dedicated electronic registry of patients with SLE who are treated with novel/biologic therapies, which will enable the detailed monitoring of drug efficacy and safety by the use of validated clinical instruments (eg, SLEDAI-2000, CLASI, RDCI, MedDRA). Moreover, the registry will help to assess the burden of the disease (severe lupus, flares, organ damage, comorbidities) among contemporary SLE patients who are seen at large Rheumatology Centres in Greece, as well as the long-term retention rates of the biological agents used in SLE such as belimumab. Importantly, the successful pilot implemen-
tation of the registry could pave the way for establishing broader collaborative projects at a national level.

**FUNDING**

This study is funded in by the Pancretan Health Association and by the Hellenic Society of Rheumatology and Professionals Union of Rheumatologists of Greece (protocol number 852).

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

**REFERENCES**

1. Adamichou C, Bertias G. Flares in systemic lupus erythematosus: diagnosis, risk factors and preventive strategies. Mediterr J Rheumatol 2017;28:4-8. [https://doi.org/10.31138/mjr.28.1.4]
2. Fanouriakis A, Bertias G. Changing paradigms in the treatment of systemic lupus erythematosus. Lupus Sci Med 2019;6:e000310. [https://doi.org/10.1136/lupus-2018-000310] [PMID: 31168398] [PMCID: PMC6519431]
3. Al Sawah S, Zhang X, Zhu B, Magder LS, Foster SA, Iikuni N, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins Lupus Cohort. Lupus Sci Med 2015;2:e000066. [https://doi.org/10.1136/lupus-2014-000066] [PMID: 25981455] [PMCID: PMC4378372]
4. Dorner T, Furie R. Novel paradigms in systemic lupus erythematosus. Lancet 2019;393:2344-58. [https://doi.org/10.1016/S0140-6736(19)30546-4] [PMID: 31180031]
5. Tsilicos K, Gladman DD, Su J, Urowitz MB. Mycophenolate Mofetil in Nonrenal Manifestations of Systemic Lupus Erythematosus: An Observational Cohort Study. J Rheumatol 2016;43:552-58. [https://doi.org/10.3899/jrheum.150779] [PMID: 26773121]
6. Fanouriakis A, Adamichou C, Koutsouviti S, Panopoulos S, Staveri C, Klagou A, et al. Low disease activity irrespecitive of serologic status at baseline-associated with reduction of corticosteroid dose and number of flares in patients with systemic lupus erythematosus treated with belimumab: A real-life observational study. Semin Arthritis Rheum 2018;48:467-74. [https://doi.org/10.1016/j. semarthritis.2018.02.014] [PMID: 29553548]
7. McCarthy EM, Sutton E, Nesbit S, White J, Parker B, Jayne D, et al. Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. Rheumatology (Oxford) 2018;57:470-9. [https://doi.org/10.1093/rheumatology/kex395] [PMID: 29216398] [PMCID: PMC5850287]
8. GlaxoSmithKline. https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-headline-results-in-phase-3-study-of-benlysta-in-patients-with-lupus-nephritis/. Accessed 2019.
9. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med 2020;382:211-21. [https://doi.org/10.1056/NEJMoai1912196] [PMID: 31851795]
10. Rovin BH, Solomons N, Pendergraft WF 3rd, Dooley MA, Tumlin J, Romero-Diaz J, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging vxicoparin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int 2019;95:219-31. [https://doi.org/10.1016/j.kint.2018.08.025] [PMID: 30420324]
11. Schindler T, Rovin B, Furie R, Leandro M, Clark M, Brunetta P, et al. ABO243 Nobilety, A Phase 2 Trial To Assess The Safety and Efficacy of Obinutuzumab, A Novel Type 2 Anti-CD20 Monoclonal Antibody (MAB), in Patients (PTS) with IIS/RPS Class III or IV Lupus Nephritis (LN). Ann Rheum Dis 2017;76:1051-2,1051. [https://doi.org/10.1136/annrheumdis-2017-013267]
Development and Implementation of a Pilot Registry for Monitoring the Efficacy and Safety of Novel Therapies in Patients with Systemic Lupus Erythematosus

Epidemiology and Surveillance Registry. Lupus 2019;28:104-13. [https://doi.org/10.1177/0961203318816820] [PMID: 30522390]

26. Gergianaki I, Fanouriakis A, Repa A, Tzanakakis M, Adamichou C, Pompeiri A, et al. Epidemiology and burden of systemic lupus erythematosus in a Southern European population: data from the community-based lupus registry of Crete, Greece. Ann Rheum Dis 2017;76:1992-2000. [https://doi.org/10.1136/annrheumdis-2017-211206] [PMID: 28730511]

27. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288-91. [PMID: 11838846]

28. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005;142:953-62. [https://doi.org/10.7326/0003-4819-142-12_part_1-200506210-00004] [PMID: 15968009]

29. Albrecht J, Werth VP. Development of the CLASI as an outcome instrument for cutaneous lupus erythematosus. Dermatol Ther 2007;20:93-101. [https://doi.org/10.1111/j.1529-8019.2007.00117.x] [PMID: 17537137]

30. Franklyn K, Lau CS, Navarra SV, Louthrenoo W, Lateef A, Hamijoyo L, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis 2016;75:1615-21. [https://doi.org/10.1136/annrheumdis-2015-207726] [PMID: 26458737]

31. van Vollenhoven R, Voskuyl A, Bertsias G, Aranow C, Artinger M, Arnaud L, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). Ann Rheum Dis 2017;76:554-61. [https://doi.org/10.1136/annrheumdis-2016-209519] [PMID: 27884822]

32. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363-9. [https://doi.org/10.1002/art.1780390303] [PMID: 8607884]

33. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45. [https://doi.org/10.1002/art.1780230202] [PMID: 7362664]

34. England BP, Sayles H, Mikuls TR, Johnson DS, Michaud K. Validation of the rheumatic disease comorbidity index. Arthritis Care Res (Hoboken) 2015;67:865-72. [https://doi.org/10.1002acr.22456] [PMID: 25186344]