Joint Damage Progression in Patients with Rheumatoid Arthritis in Clinical Remission. Do Biologics Perform Better Than Synthetic Antirheumatic Drugs?

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ABSTRACT. ***Objective.*** Randomized controlled studies have demonstrated protective advantages of biologic therapies over the synthetic disease-modifying antirheumatic drugs (DMARD) in slowing joint damage progression in patients with rheumatoid arthritis (RA). This effect appears to be largely independent of the clinical disease control. We measured the rate of radiographic progression in patients with RA in clinical remission treated with synthetic versus biologic DMARD.

Methods. This is an observational cohort study of patients with RA in clinical remission, nested within the Swiss Clinical Quality Management in Rheumatoid Arthritis (SCQM-RA) Registry. The primary study outcome was the rate of radiographic progression (Ratingen erosion score), and a secondary outcome was functional disability [Health Assessment Questionnaire-Disability Index (HAQ-DI)] progression. We compared the rate of progression between synthetic and biologic DMARD using a multivariate regression model for longitudinal data, adjusting for potential confounders.

Results. A total of 2055 patients in the SCQM-RA registry were in remission at least once from 1999 to 2012 and met the study inclusion criteria. Baseline characteristics of patients in remission receiving synthetic and biologic DMARD were not significantly different in terms of prognostic factors for joint damage progression. During followup, erosion progression differed significantly between the 2 groups [1.4% (95% CI: 1.1–1.6) vs 0.9% (95% CI: 0.5–1.2) of progression over 3 years, respectively, $p < 0.001$], with less damage progression in patients treated with biologic DMARD than with synthetic DMARD. This difference remained significant after adjusting for confounding factors. The evolution of the HAQ-DI score was also statistically better in the biologic group ($p < 0.001$).

Conclusion. This observational study confirms that the rate of structural damage progression in clinical remission is decreased taking biologics compared to synthetic DMARD. However, while the difference is statistically significant it is probably not relevant from a clinical perspective. (J Rheumatol First Release July 15 2014; doi:10.3899/jrheum.130767)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE ACTIVITY JOINT DAMAGE PROGRESSION
ANTIRHEUMATIC THERAPY REMISSION TUMOR NECROSIS FACTOR-α INHIBITORS

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E. Ciubotariu is supported by research grants from Montréal University and AMRQ (Association des Médecins Rhumatologues du Québec). A. Finckh is supported by a research grant from the Geneva University and the Swiss National Science Foundation (Grant No. 3200B0-120639). C. Gabay is supported by the Swiss National Science Foundation (Grant No. 310030-135195).

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Accepted for publication February 20, 2014.

Rheumatoid arthritis (RA) is characterized by the presence of joint inflammation and bone destruction[1]. Disease severity varies considerably among patients according to several complex genetic and environmental factors[1,2,3,4,5,6,7,8]. Depending on the level of disease activity, RA causes progressive joint destruction, deformities, and functional disability, with only a minority achieving a state of remission or low disease activity. In the era of biologic therapies and an increasing number of treatment options, remission or low disease activity have become the current targets of RA treatment[4,7,9,10].

Preventing structural joint damage remains the ultimate goal of RA treatment[6,9,11]. Prospective and retrospective cohort studies have demonstrated that even in clinical remission, some patients still experience progressive deterioration of radiographic damage[12,13]. One explanation is that

the current tools used to define clinical remission [28-joint Disease Activity Score (DAS28), Simplified Disease Activity Index, Clinical Disease Activity Index, etc.] are not sensitive enough to detect low levels of synovial inflammation, leading to some degree of joint damage over time[13,14]. Thus, persistent subclinical joint inflammation might explain the apparent disconnect between clinical signs and structural damage. Subclinical inflammation may be detected with more sensitive tools, such as joint ultrasound or magnetic resonance imaging[2]. Other authors suggested that the 2 key features of RA, inflammation and joint destruction, may only partially share a common physiopathology[2,14,15]. Some treatments may interfere preferentially with the inflammatory pathways, while others may operate mainly on joint erosions and still others may intervene with both. It has been observed that the relation between disease activity and radiographic progression is seen only in patients receiving synthetic disease-modifying antirheumatic drugs (DMARD), while the relationship is disconnected in patients treated with biologic agents. Several subanalyses of randomized trials have demonstrated a distinct benefit of various biologic therapies on the radiographic progression beyond their antiinflammatory effect[16,17,18,19,20,21,22,23,24].

These observations have introduced a novel concept of radiographic remission, which may not always overlap clinical remission[9,11,14,25]. Nevertheless, the new concept of radiographic remission has not yet been validated or even clearly been defined in terms of scoring system or duration[25]. Further, targeting radiographic remission has not yet been shown to improve the patient's longterm outcomes. To the best of our knowledge, the longitudinal relationship between clinical remission and joint damage according to the type of treatment (synthetic DMARD vs biologic treatment) has not been studied outside of selected trial populations. The aim of our study is to compare the rate of radiographic damage progression while the patient receives synthetic and biologic DMARD, in RA patients in clinical remission. Our *a priori* hypothesis was that patients in remission on biologic treatments would have less damage progression over time than patients in remission taking synthetic DMARD.

MATERIALS AND METHODS

We performed a nested analysis within a prospective, longitudinal, observational cohort study of a population-based RA cohort.

Study population. The SCQM-RA register is a Swiss longitudinal cohort of patients with RA described in detail elsewhere[26]. Patients are assessed at inclusion (demographics, disease characteristics, etc.) and at regular intervals longitudinally, between 1 and 4 visits per year (disease activity, antirheumatic treatments, side effects, reasons for discontinuation, radiographs, comorbidities, etc.). Currently, the SCQM register includes over 5400 biologic treatment courses of patients with RA and about 2000 treatment courses on synthetic DMARD. Patients in the register came from diverse clinical settings, with more than 50% from private practice, 30% from nonacademic centers, and 20% from academic centers. The study population can be considered a representative sample of the Swiss RA population taking biologic therapies.

The inclusion criteria for our study were a diagnosis of RA by a board-certified rheumatologist, at least 2 consecutive sets of radiographs of hand and feet, and being in remission. Clinical remission was defined as a DAS28-erythrocyte sedimentation rate (DAS28-ESR) of ≤ 2.6. In a sensitivity analysis, we used a more stringent definition of remission, with the new American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) remission criteria[10]. The exclusion criteria were insufficient radiographs to compute a rate of progression and missing DAS28 assessments. Because remission may fluctuate over time, we restricted analysis to radiographic intervals shorter than 3 years [treatment course (TC)]. We included all patients in the database corresponding to the inclusion and exclusion criteria between January 1997 and April 2012. Ethical approval for the collection of patient data for the SCQM register was obtained by a national review board.

Outcome measures. The study's predetermined outcome was radiographic disease progression during clinical remission as measured by the annual change in radiographic damage scores. The radiographic damage was assessed prospectively on digitalized radiographs of hands and feet using a validated scoring method. The Ratingen score measures the amount of destroyed joint surface by the erosions[27,28]. Thirty-eight hand and foot joints are scored individually from 0 to 5 and combined in a single score ranging from 0 to 190. For readability, we express the erosion score as a percentage of the maximum possible erosion score (0–100%). The Ratingen scoring method has good reliability, with an intrarater intraclass correlation coefficient (ICC) of 0.8–0.9 and an interrater ICC of 0.7–0.9 and may be less susceptible to ceiling effects in advanced disease because of a true ordinal rating system[27]. The minimal detectable radiographic change for this method has been determined to be 3.3% of the maximum score[11,25,27,29].

Operationally, we defined a radiographic interval (TC) in remission if at least 50% of the observations in the time interval were in remission. To explore the robustness of this definition, we performed a sensitivity analysis including only radiographic intervals in remission at least 80% of time.

A secondary outcome was progression of functional disability as measured by change in Health Assessment Questionnaire Disability Index (HAQ-DI, Stanford). The HAQ-DI is the most commonly used functional status questionnaire in RA and has been demonstrated to predict future disability and mortality with a minimal detectable change of 0.19–0.24 and a clinically detectable improvement of 0.24[30].

Exposure of interest. The exposure of interest for our study was the type of treatment used to obtain clinical remission. Exposure variables were synthetic and biologic DMARD. Synthetic DMARD were defined as methotrexate (MTX), leflunomide (LEF), sulfasalazine (SSZ), hydroxychloroquine (HCQ), or other conventional DMARD (parenteral gold, cyclosporine, azathioprine). Glucocorticoids can have an effect on slowing of radiologic joint damage progression[5] and given the significant number of patients in remission with glucocorticoids as unique remissive therapy, we decided to include them in the conventional DMARD group. Biologic DMARD were defined as adalimumab (ADA), etanercept (ETN), infliximab (IFX), tocilizumab (TCZ), rituximab (RTX), and abatacept (ABA).

Statistical analysis. We estimated the statistical power based on previously published data on rates of radiographic progression in this database, with the objective of being able to detect a 2-sided difference of at least 0.2 Ratingen score units in rates of radiographic damage progression per year, similar to the difference detected between anti-tumor necrosis factor (TNF) agents with or without synthetic DMARD[18]. Assuming a statistical power of 90%, a type I error probability of 0.05, and a ratio of ~1:2 between DMARD remission and biologic remission, 273 patients were needed to demonstrate a significant difference in the rate of radiographic progression.

Baseline disease and treatment characteristics were compared between the synthetic and biologic DMARD groups using conventional descriptive

statistics. The significance of differences in baseline characteristics was assessed with the Student t test for normally distributed mean variables of continuous variables, the Kruskal-Wallis test for non-normally distributed variables, and Pearson's chi-square test for dichotomous variables. Because differences in disease characteristics may greatly influence radiographic damage progression, we used a mixed linear regression model for longitudinal data, adjusting for potential confounding factors, and an unstructured covariance structure. In particular, we adjusted for differences in disease characteristics [rheumatoid factor, disease duration, baseline radiographic damage, functional status (HAQ) disease activity (DAS28)], treatment characteristics (glucocorticoid use, type of synthetic DMARD use), and patient characteristics (age, sex, and socioeconomic status as measured by years of education). We used the model's mean estimates to produce Figure 1. The analysis was reproduced with alternative definitions of remission and time in remission for sensitivity analyses (available from the authors on request). The analysis was performed with STATA V.11 (Stata Statistical Software).

RESULTS

Baseline. Of the ~7000 patients with RA followed longitudinally in the SCQM-RA registry, a total of 2055 were in remission, at least during 1 period. About 12% of patients (n = 255) experienced remission periods while receiving both synthetic and biologic DMARD therapy, contributing a total of 2332 treatment periods for analysis; 1398 received synthetic DMARD and 934 biologic DMARD. On average, patients contributed 3 treatment periods in remission, lasting a median of 12.5 months [interquartile range (IQR): 11.7–17.0].

No significant differences in baseline disease characteristics between synthetic and biologic DMARD groups were observed (Table 1), in particular for key prognostic factors of radiographic disease progression such as education level or disease activity (DAS28). However, at baseline, disease duration was longer in the biologic DMARD compared to the synthetic DMARD group (median 5.8 and 3 yrs, respectively, $p < 0.001$). Rheumatoid factor was more prevalent (78% vs 73%, $p = 0.02$) and tender and swollen joint counts slightly higher (Table 1). The baseline erosion score (ERO) was significantly higher in the biologic DMARD than in the synthetic DMARD group (median 4.7 vs 2.6, $p < 0.001$), but the estimated rate of ERO progression at baseline was similar in the 2 groups (median 1.06 in the biologic vs 1.07 in synthetic group, $p = 0.5$), suggesting that radiographic severity was balanced between groups at baseline. For synthetic DMARD, MTX was the most prescribed treatment (77%). The most commonly used biologic DMARD were etanercept (33.5%) and adalimumab (32%), and 76% of patients were receiving a biologic therapy combined with synthetic DMARD. While patients could theoretically discontinue their antirheumatic therapy during the treatment course, this was a rare event because 97% of biologic DMARD were continued during the entire time interval in remission. Surprisingly, 46% of patients receiving synthetic DMARD and 44% receiving biologics were using

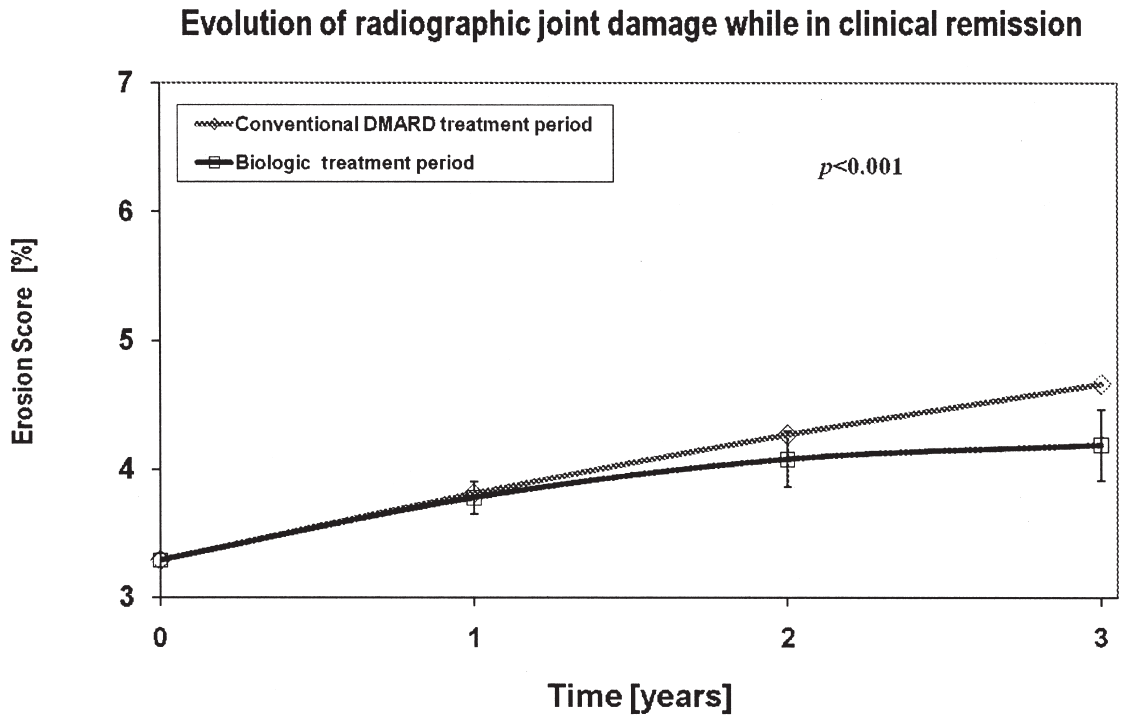

Figure 1. Progression of mean radiographic erosion in patients clinically in remission receiving conventional and biologic disease-modifying antirheumatic drugs (DMARD); 95% CI are displayed as the vertical lines. The analysis is adjusted for confounding factors (see statistical analysis). Erosion score is expressed as a percentage of maximum damage score using the Ratingen score.

Table 1. Patient characteristics.

Baseline Characteristics	Biologic Treatment Course[&], n = 934	Conventional Treatment Course[&], n = 1398	p
Age, yrs, median (SEM)	58.8 (13.4)	60.7 (13.7)	0.9
Treatment period, mos, median (IQR)	12.6 (11–16)	12.4 (11–15)	
Treatment period with biologic DMARD, mean (SEM)*	97 (0.13)	—	
No. radiographs, mean	3.02	3.42	
Sex, % male	26	29	0.09
Disease duration, yrs, median (IQR)	5.8 (2.4–12.4)	3.03 (0.8–8.3)	0.0001
Rheumatoid factor, mean	78	73	0.018
ACPA mean**	66	64	0.53
Radiographic damage progression, median (IQR)***	1.06 (0.42–2.08)	1.07 (0.31–2.53)	0.52
Erosion score, %, median (IQR)	4.7 (1.8–15.6)	2.6 (0.9–7.8)	0.0001
DAS28 (SEM) ****	3.21 (1.37)	3.11 (1.32)	0.24
SJC, mean (SD)	4.3 (5.2)	3.6 (4.6)	0.0001
TJC, mean (SD)	3.6 (5.2)	3.1 (4.7)	0.0001
HAQ, mean (SD)	0.8 (0.6)	0.6 (0.6)	0.3
BMI, mean (SD)	24.7 (4.5)	25.1 (4.8)	0.2
Smoking, %	52	58.7	0.35
R-OH, %	66	64	0.34
Type of biologic DMARD, mean			
ADA, %	31.9	—	
ETN, %	33.5	—	
IFX, %	23	—	
TCZ, %	3.6	—	
RTX, %	5.4	—	
ABA, %	2.6	—	
Type of conventional DMARD[+], mean			
HCQ, %	5.4	14.7	0.0001
MTX, %	62.9	76.8	0.084
LEF, %	13.9	10.9	0.044
SSZ, %	9.1	15.8	0.0001
Other, %	0.1	0.1	0.1
No DMARD, %	24.8	11	0.0001
Glucocorticoid use, %, mean	44	42	0.80
No. previous biologic DMARD, mean	1	0	0.0001
Education, yrs, median (IQR)	12 (12–12)	12 (12–12)	0.3

*Time (%) taking biologic DMARD per treatment period; **ACPA were available for 66% of patients; ***Estimated radiographic damage progression at baseline (RS%/yr); ****DAS28 ESR; [+]Total percent of individual DMARD may exceed 100%, because of combination of DMARD; [&]TC: radiographic intervals in remission. Radiographic damage at baseline: Estimated baseline radiographic progression at baseline. ACPA: anticyclic citrullinated peptide antibodies; SJC: swollen joint count; TJC: tender joint count; HAQ: Health Assessment Questionnaire; BMI: body mass index; R-OH: alcohol intake; DMARD: disease-modifying antirheumatic drugs; ADA: adalimumab; ETN: etanercept; IFX: infliximab; TCZ: tocilizumab; RTX: rituximab; ABA: abatacept; HCQ: hydroxychloroquine; MTX: methotrexate; LEF: leflunomide; SSZ: sulfasalazine; IQR: interquartile range; DAS28: 28-joint Disease Activity Score.

concomitant oral glucocorticoids while in clinical remission, and 11% of patients in the synthetic DMARD group were receiving the glucocorticoid cortisone as unique remission therapy. Glucocorticoid use did not influence the rate of radiographic damage progression in this population ($p = 0.80$).

Radiographic damage progression. In the crude unadjusted analyses, erosion progression differed significantly between the 2 groups ($p < 0.001$), with less damage progression in the biologic DMARD than in the synthetic DMARD group [0.8% vs 1.3% ERO progression over 3 years, respectively ($p < 0.001$)]. When results were adjusted for potential confounding factors (disease duration, age, sex, HAQ, DAS28, BMI, ERO, educational level, type of conventional DMARD, and glucocorticoid use) the difference remained significant [3 years ERO progression of 0.9% (95% CI: 0.5–1.2) vs 1.37% (95% CI: 1.1–1.6; Figure 1)]. In both groups a substantial percentage of patients were using concomitant low-dose glucocorticoids while in remission. We analyzed the effects of glucocorticoid use on radiographic

progression and found no significant influence of glucocorticoid use on damage progression in this population (p = 0.80). We also tested for interaction (effect modification) by glucocorticoid use and could not demonstrate that the effect on radiographic progression of biologics versus synthetic DMARD was modified by concomitant use of glucocorticoids (p = 0.58).

In sensitivity analyses, we used more stringent definitions of remission and found qualitatively the same results, suggesting that the choice of definition used for remission did not influence these results. When remission was required to be present for at least 80% of all visits during the radiographic interval, the 3-year ERO progression rate was –0.17% (95% CI: –0.6 to 0.3) in the biologic DMARD versus 0.6% (95% CI: 0.2 to 1.1) in the synthetic DMARD group (p < 0.001). When remission was defined with the new ACR/EULAR as remission criteria, the 3-year progression rate was 0.3% (95% CI: –0.1 to 0.7) and 0.9% (95% CI: 0.5 to 1.3) in the biologic versus synthetic DMARD group, respectively (p < 0.001). While the differences in radiographic progression were statistically significant [difference in ERO progression after 3 years of 0.47 (95% CI: 0.14 to 0.8)], the effect size was small.

Secondary outcome. To estimate the clinical effect of the radiographic changes between groups, we examined the evolution of functional disability (HAQ-DI). After adjusting for the same potential confounders, we found a small but statistically significant difference at 3 years in favor of biologic DMARD, with a –0.18 (95% CI: –0.22 to 0.14) improvement versus –0.1 (95% CI: –0.13 to –0.071) improvement in the conventional DMARD group (p < 0.001). While the functional disability results confirmed the radiographic findings, the effect size of 0.08 HAQ-DI units was below the clinically detectable improvement threshold of 0.24.

DISCUSSION

In this cohort of patients with RA who were in remission, we found significantly lower rates of radiographic progression in patients treated with biologic versus synthetic DMARD, a difference that was not explained by disease duration, disease severity, or other key disease characteristics. The trend was similar for functional disability (HAQ-DI), suggesting a possible clinical effect of radiographic findings. However, the differences in the rate of radiographic progression remained small and probably clinically irrelevant after 3 years, far from the minimal detectable change threshold of 3.3% of the maximal Ratingen score[27,29]. A similar argument can be made for the HAQ-DI evolution, where a 0.08 HAQ units difference after 3 years is far from the minimum clinical difference threshold of 0.24[30]. Therefore, the difference in disease progression between biologic and conventional DMARD should be considered negligible from a clinical or a patient perspective.

Biologic therapies have demonstrated a clear advantage over conventional DMARD in their capacity to prevent radiographic damage progression. In particular, radiographic damage is no longer linearly associated with clinical response to therapy with biologic agents, which has often been coined a "disconnect between inflammation and structural damage."[27] This phenomenon has been demonstrated with almost all biologic agents; first with anti-TNF and more recently with RTX, TCZ, and ABA, all of which showed a distinct benefit on joint damage progression regardless of clinical effects. However, these studies were posthoc analyses of randomized controlled trials (RCT) in heterogeneous groups of patients with RA. Only a few publications have investigated damage progression in clinical remission, but these studies have not specifically examined the effects of the type of treatment used to induce remission. Further, the generalizability of results from RCT is limited, warranting analysis of real-life patients in remission. In RCT with biologic DMARD, radiologic progression has often been analyzed in all patients without subanalysis according to clinical state. In 1 trial of a biologic agent[19], the radiologic remission (total Sharp score < 0.5) was attained in 85% of patients in the combination therapy group (MTX + biologic DMARD) vs 55% taking MTX alone.

Further, prospective data are lacking on the clinical relevance of these differences in damage progression[31,32]. In the absence of any trial directly comparing joint damage progression during remission by type of treatment, we analyzed observational data for the rate of radiographic progression between conventional and biologic DMARD.

Our study has potential limitations inherent to observational data when comparing effectiveness of different treatment strategies. One very real limitation is potential selection bias. In the SCQM registry, patients taking biologic DMARD are overrepresented compared to synthetic DMARD. However, the baseline characteristics of patients with RA in remission with both types of agents suggest similar prognostic factors. Further, given that patients with more severe disease are more likely to receive biologic therapies, the results would have been biased toward the null, so that the unbiased difference might have been slightly larger than what we observed. While established confounding factors were adjusted for in the statistical analysis, we acknowledge the possibility of other potential unmeasured or residual confounding. There is no unanimity among researchers on which methods to use when it comes to determining the status of clinical remission. We addressed this issue by applying several different methods for defining remission and found that each of these various approaches yielded similar results, which supports the strength of our findings. The primary endpoint of the study was the radiographic erosion progression, and we do not have any data on the effect of

treatment type on joint space narrowing. The followup on remission was relatively limited and we cannot exclude that these minor differences could become more clinically relevant over a longer period of followup. Longer cohort studies are warranted to address the clinical relevance of radiographic remission more clearly. The strength of this study is the large population-based cohort, which allowed us to demonstrate minor differences. The groups were analyzed prospectively with a well-validated radiographic damage scoring method.

Our data suggest that clinical remission is a realistic treatment target for the management of RA. Our results demonstrate that once patients achieve a state of clinical remission, whatever the treatment used to obtain this state, we do not find any clinically meaningful advantage of biotherapies over synthetic DMARD with respect to joint damage progression or functional disability. Overall, it seems that reaching the remission target is more relevant than the treatment used to reach remission. However, we must also keep in mind that our targets are not necessarily the patient's targets. Patients are less focused on damage progression and more focused on quality of life and being free of pain.

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