# ANIFROLUMAB IN REFRACTORY SYSTEMIC LUPUS ERYTHEMATOSUS:

# A REAL-LIFE, MULTICENTER STUDY

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**Key Messages**

- What is already known about this subject?

  Real-world data on Anifrolumab use in Systemic Lupus Erythematosus (SLE) are limited.

- What does this study add?

  This study describes a multicenter real-world experience on the use of Anifrolumab in refractory SLE treated in a compassionate use program.

- How might this impact on clinical practice?

  This study provides a real-world experience on the use of Anifrolumab in refractory SLE patients, confirming its rapid effectiveness and an overall acceptable safety profile in difficult to treat patients.

## Abstract

### Background

Real-world data on Anifrolumab (ANI) use are limited and mainly focused on cutaneous Systemic Lupus Erythematosus (SLE) manifestations.

### Objectives

To report the real-world experience on the use of ANI in refractory SLE.

### Methods

Multicenter retrospective study involving 9 Italian SLE referral centers participating in a compassionate use program for the use of ANI in active adult SLE patients in whom all the available treatment choices failed, were not tolerated or contraindicated.

At baseline, at 1, 3, 6, 9 and 12 months of treatment, overall and organ specific disease activity, flares, daily glucocorticoid (GC) dose, and adverse events were recorded.

### Results

A total of 26 patients were enrolled. At 4 weeks after starting ANI, a significant decrease in SLEDAI-2K ($p=0.005$), SLE-DAS ($p=0.005$) and PGA ($p=0.001$) was recorded, and the same trend was maintained over time.

A significant reduction in CLASI-activity ($p<0.001$) and in tender ($p=0.026$) and swollen ($p=0.017$) joint count was also recorded.

At 3 months of follow-up, 33% of patients already achieved a remission state, while 46% were in LLDAS; at 6 months, 50% were in remission and 80% in LLDAS. A significant reduction in the mean GC daily dose was observed, starting from week 4 ($p=0.04$).

A total of 4 disease flares according to the SELENA-SLEDAI Flare Index were recorded (three mild-moderate and one severe). Overall, 4 out of 20 patients with at least 24 weeks of follow-up (20%) were considered “non responders”.

### Conclusions

This study provides a real-world experience on the use of ANI in refractory SLE patients, confirming its rapid effectiveness and an overall acceptable safety profile.

**Introduction**

In recent years, type 1 interferon pathway gained a central role in SLE pathogenesis, and it became an important treatment target. (1)

Anifrolumab (ANI), a fully human monoclonal antibody against type I interferon receptor, has been recently approved in several countries for the treatment of moderate to severe SLE as an add-on treatment to standard therapy.

Data from phase II and III clinical trials demonstrated the efficacy of ANI against global disease activity measures as well as on a number of other clinically relevant endpoints, including oral glucocorticoids (GCs) tapering, flare rates, cutaneous responses, and joint counts. (2-4)

As of this writing, real world data (RWD) on its use are limited to small cases series and case reports mainly focused on cutaneous SLE manifestations; overall, RWD confirmed the rapid efficacy on refractory cutaneous manifestations, with little attention to systemic disease involvement. (5-10)

In this study we aimed at reporting a multicenter real–world experience on the use of ANI in refractory SLE treated in a compassionate use program.

**Methods**

This is a multicenter retrospective study involving 9 Italian referral centers for SLE (Pisa, Padova, Milano, Roma, Cagliari, Napoli, Udine, Firenze, Bari) participating in a compassionate use program for the use of ANI in active adult SLE patients in whom all the available treatment choices failed, were not tolerated or contraindicated.

Consecutive patients fulfilling available classification criteria for SLE and meeting criteria for compassionate use of ANI were enrolled in the study.

Demographic data, clinical and treatment history and SLICC Damage Index (SDI) were retrieved from clinical charts.

At baseline, at one month and then every 3 months of treatment SLE-disease activity index 2000 (SLEDAI-2K), SLE-Disease Activity Score (SLE-DAS), daily prednisone dose, number of tender (Tj) and swollen (Sj) joints, Cutaneous LE Disease Area and Severity Index-activity (CLASI-A) and CLASI-damage (CLASI-D), and Physician Global Assessment (PGA) were recorded.

Remission state (according to 2021 DORIS definition) and low disease activity state (according to LLDAS definition) were assessed at 3, 6 and 12 months (11, 12); among patients with at least 6 months of follow-up, non responders were defined as patients who did not achieve at least LLDAS at last follow-up visit or who withdrew the treatment because of flare or persistently active disease.

Adverse events (AEs) were recorded at each visit.

From the six month of ANI treatment onward, the occurrence of disease flare was evaluated according to the SELENA-SLEDAI Flare Index (SFI) every 3 months.

The study was approved by the Comitato Etico Area Vasta Nord Ovest and all the patients gave consent for their medical information to be published.

*Statistical analysis*

Continuous variables were described as median and 25-75 interquartile range (IQR) or as mean and standard deviation (SD), as appropriate. Categorical variables were reported as proportions. Cross-tabulated data were analyzed using paired samples Wilcoxon test, whereas intergroup comparisons were performed using Mann-Whitney test. Statistical analysis was performed by using IBM® SPSS® Statistics (Version 29.0) statistic software package. P-values $<0.05$ were considered statistically significant.

**Results**

*Baseline data*

Twenty-six patients were enrolled in the analysis; demographics and clinical characteristics are summarized in Table 1.

Briefly, patients were predominantly females (N=24, 92%) and Caucasians (N=24, 92%), with a median age of 47.5 years (min. 25 – max. 69) and a median disease duration of 12.5 years (min. 5 – max. 34) at enrollment.

Ninety-six percent of patients had a history of articular involvement, 92% of mucocutaneous manifestations, 61% of haematological manifestations, 35% of lupus nephritis (of which seven cases biopsy-proven and the remaining two defined on the basis of persistent proteinuria in the absence of other reasonable causes), 27% of serositis, and 11% of neuropsychiatric involvement.

Twenty-three percent had a concomitant antiphospholipid syndrome and 7% an overlapping Sjögren's syndrome.

At baseline, 53% had an SDI>0 (median 2, min. 1 – max. 6).

All patients had been previously treated with immunosuppressants with a median number of previous immunosuppressive therapies of 4 (min. 1 – max. 8); the median cumulative dose of GC (prednisone-equivalent) was variable, ranging from 1.2 to 90 g (median 13 g). Eighty percent of patients had failed Belimumab (N=21) and 19% Rituximab (N=5); all patients who had not responded to Rituximab were also non-responders to Belimumab.

Clinical manifestations and ongoing therapies at the time of ANI starting are summarized in Table 1. Briefly, all patients were active at enrollment and reasons for adding ANI to the background therapies were a persistently active disease in 17 patients (65%) or a disease flare in 9 patients (35%). A detailed description of the characteristics of the two patient groups at baseline is reported in Table S1 (supplementary materials).

The most frequent active manifestations at enrollment were mucocutaneous (73%), articular (46%), and haematological (27%).

Twenty-one patients (81%) presented active serology at baseline (anti-dsDNA positivity and/or hypocomplementemia).

As far as concomitant treatment is concerned, the majority of patients was receiving conventional immunosuppressive drugs (N=23, 88%), GC (N=24, 92%), and antimalarials (N=21, 81%). The median daily dosage of oral GC at enrollment was 7.5 mg (min. 0 – max. 25) and no GC pulses were used. Of note, 3 patients were only on antimalarials or GC because of failure or intolerance to several previous immunosuppressive therapies (Table 1).

*Efficacy evaluation*

Patients were followed for a median of 36 weeks (min. 4 – max. 72).

During the follow-up, at 1 month after starting ANI, a significant decrease in both SLEDAI-2K and SLE-DAS global activity indices was recorded (baseline mean±SD SLEDAI-2K 8.0±4.1 vs 6.2±3.4, p=0.005; baseline mean±SD SLE-DAS 9.3±5.4 vs 6.3±4.2, p=0.005). The same trend was maintained over time (Figure 1a and Table 2).

In parallel, also PGA significantly decreased from a baseline mean of 1.3±0.5 to 1±0.5 after one month (p=0.001).

As far as patients with active skin and joint involvement, a significant reduction in the CLASI-A and in the joint count was also recorded as summarized in Figure 1b-c and in Table 2. The improvement was maintained through the entire follow-up. Baseline haematological manifestations improved in 3 out of 6 patients (50%) by week 12 and this improvement was maintained over the follow-up.

Interestingly, the percentage of patients with active serology slightly decreased over time from week 24 of treatment (63% at week 24, 54% at week 36 and 57% at week 48) and a complete normalization of serology was observed in 43% of patients at the last follow-up.

As far as treatment outcomes is concerned, at 3 months of follow-up, 8/24 (33%) patients already achieved a remission state while 11/24 (46%) were in LLDAS; at 6 months, 10/20 (50%) were in remission and 16/20 (80%) were in LLDAS. Among the patients who completed 12 months of follow-up, 6/7 (86%) were in remission at this time point, being a daily GC dose >5 mg the criterion for not achieving remission in one patient. A decrease in the mean daily dose of GC was observed, and it was statistically significant at 1 month (7.6±5.0 mg/day vs 6.4±4.9 mg/day, p=0.04); thereafter the difference lost its significance (Figure 1d and Table 2).

A subgroup analysis showed no significant differences in treatment efficacy between patients with SDI=0 and SDI>0 at baseline. The detailed trend of the efficacy measures over time in the two patient groups is shown in Table S2 (supplementary materials).

During the follow-up period, a total of 4 disease flares according to the SFI were recorded (three mild-moderate and one severe): 1 flare at week 4 (a new-onset pericarditis in a patient with no previous history of serositis), 2 flares at week 24 (one with leucopenia and thrombocytopenia and one with new-onset proteinuria and a diagnosis of lupus nephritis), and 1 flare at week 36 (with arthritis and thrombocytopenia). Two out of 4 flares, specifically pericarditis and lupus nephritis, required treatment discontinuation. In particular, the patient with new-onset proteinuria, who had no previous history of renal involvement, underwent a kidney biopsy that proved a class IV lupus nephritis; consequently, ANI treatment was discontinued in favor of induction therapy with cyclophosphamide.

Overall, 4 out of 20 patients with at least 24 weeks of follow-up (20%) were defined “non responders”.

*Safety*

A total of 27 adverse events were recorded during the entire study period; of these, 23 (85%) were infections, generally mild, including three cases of oligosymptomatic COVID-19, one COVID-19 case that required hospitalization and one case of multi-metameric Varicella Zoster reactivation in a patient who later also developed cellulitis of a lower limb. Recurrent severe infections were the reason for treatment discontinuation in this last patient. In some other cases, a temporary treatment suspension was required.

If all patients had previously been vaccinated for SARS-CoV-2 (median number of vaccine doses 3, IQR 2-3), only 10/26 (39%) had received the Herpes Zoster vaccine; of note, the patient who developed multi-metameric Herpes Zoster was among the unvaccinated patients.

Among the other adverse events, one case of pulmonary thromboembolism affecting a 66-year-old male patient was registered.

Details of adverse events and timing are summarized in Table 3.

**Discussion**

In this study we describe the real-world experience on the use on ANI in active SLE patients enrolled in a compassionate use program for refractory cases.

As expected, according to the compassionate use requirements, patients included in this study displayed an active disease despite previous treatments, including biologics. Overall, the study population was characterized by a long mean disease duration and a significant organ damage at ANI initiation, with over half of patients exhibiting an SDI>0 at baseline, despite a quite young mean age.

In this analysis, we showed a significant improvement in all the efficacy measures including global activity scores (SLEDAI-2K, SLE-DAS, PGA) and organ specific measures (CLASI-A, joint count); interestingly, the first significant improvement was observed as early as the first month of therapy and was maintained over time in most of the cases despite concomitant tapering of GCs.

Indeed, after 6 months of treatment, 50% and 80% of patients were in remission and LLDAS, respectively. Some early signs of efficacy could be intercepted even before, as already at 3-month follow-up 33% of patients were in remission and 46% in LLDAS.

On the other hand, 4 flares were recorded during the follow-up, one of which was severe and required treatment discontinuation. Moreover, overall, 20% of patients of this series could be considered “non responders”.

These data are in line with what reported in clinical trials and confirm also in the real world the rapid treatment response and ANI effectiveness on a range of clinical manifestations.

Indeed, in a recent *post-hoc* analysis of pooled data from the TULIP-1 and TULIP-2 trials, from as early as week 8 the proportion of patients with a BICLA and CLASI-A response was significantly greater with ANI than placebo, and a greater reduction in GC dosage compared with placebo by week 20 was also reported. (13)

Another interesting aspect of this analysis relies on the fact that the introduction of ANI to tackle disease activity was associated to very low doses of oral GCs; moreover, the quick response obtained allowed a further GC reduction over time; indeed, at 12 weeks of follow-up 63% of patients was receiving ≤5 mg prednisone/day.

This is a very important aspect that might suggest the use of the drug to rapidly control disease activity avoiding high doses of GCs.

The GC-sparing effect of ANI have been clearly demonstrated in clinical trials. The present data further reinforce this result from a real-life perspective and might encourage physicians to minimize the GC dosage also in their active patients while prescribing ANI. (14)

To the best of our knowledge, this is the first report on the real-life use of ANI in a cohort of SLE patients following a well-defined data collection approach.

Moreover, although several case reports and case series described the effectiveness of ANI on a wide range of muco-cutaneous manifestations, to date, less data are available on the real-world use of the drug in other disease manifestations. In our case series, haematological manifestations and arthritis were present at enrollment in 27% and 46% of patients, respectively. Thus, these patients’ sample is highly representative of the complexity and the variability of the clinical picture of the disease and very much illustrative of the type of patient for whom ANI finds indication.

As far as the treatment safety is concerned, several adverse events were recorded, with few being moderate or severe; indeed, treatment discontinuation has been rare. Similarly to what observed in clinical trials, infections were the most frequent adverse events. This is not surprising given that patients included in this analysis were active, with long disease duration and significant organ damage, on concomitant treatment with GC and conventional immunosuppressants, all considered important risk factors for infections in SLE. (15)

In conclusion, this study provides a real-world experience on the use of ANI in refractory SLE patients, confirming its effectiveness and the overall acceptable safety profile. Moreover, these data also provide some new and interesting insights to be further developed and tested in larger studies.

**Competing interest**: none

**Contributorship statement**: CT, LQ, FC, FC, AC, LD, AD, MM provided a substantial contribution to the conception of the work; revised the draft critically for important intellectual content; approved the version of the manuscript to be published and agreed to be accountable for all aspects of the work.

CT, CC, MZ, LM, MP, FC, SF, GDM, LC, GE, MG, FT, GAR, EC, GG, LP, MP, MLU, EB, provided a substantial contribution to the conception of the work, to the the acquisition, analysis, and interpretation of data, drafted the work, approved the final version to be published and agreed to be accountable for all aspects of the work.

**Founding**: none

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**Ethical approval:** The study was approved by Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, approval number 24198**.**

**Data sharing statement:** All data relevant to the study are included in the article or uploaded as supplementary information.

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**Figures legend**

Fig. 1a: global activity indices over time

Legend:

* p=0.005 between T0 and T4

§ p=0.002 between T0 and T36

Fig. 1b: CLASI-A over time

Legend:

* p<0.001 between T0 and T4

§ p=0.012 between T0 and T36

Fig. 1c: joint count over time

Legend:

* p=0.026 for Tj and p=0.017 for Sj between T0 and T4

§ p=0.012 for Tj and p=0.043 for Sj between T0 and T36

Fig. 1d: mean GCs daily dose (prednisone-equivalent)

Legend:

* p=0.04 between T0 and T4

§ p=n.s. between T0 and T36

**Tables**

**Table 1. Characteristics of the cohort at baseline (N=26).**

| | |
|---|---|
| **Female** | 24 (92%) |
| **Age**[1] [years] | 48 (38-59) |
| **Disease duration**[1] [years] | 13 (8-23) |
| **Ethnicity: Caucasian / non-Caucasian** | 24 (92%) / 2 (8%) |
| **Organ involvement** *[cumulative / ongoing]* | |
| Mucocutaneous | 24 (92%) / 19 (73%) |
| Articular | 25 (96%) / 12 (46%) |
| Haematological | 16 (62%) / 7 (27%) |
| Renal | 9 (35%) / 1 (4%) |
| Serositis | 7 (27%) / 0 |
| Neuropsychiatric | 3 (12%) / 0 |
| **Active serology at baseline (anti-dsDNA and/or hypocomplementemia)** | 21 (81%) |
| **Secondary Antiphospholipid Syndrome** | 6 (23%) |
| **Secondary Sjögren's Syndrome** | 2 (8%) |
| **Cumulative glucocorticoids (GCs) dosage**[1] [g] | 13 (10-19) |
| **N° of previous immunosuppressants**[1] | 4 (3-5) |
| **Concomitant therapies** | |
| Hydroxychloroquine | 21 (81%) |
| Glucocorticoids | 24 (92%) |
| GCs daily dose[1] [mg prednisone-equivalent] | 7.3 (5-10) |
| Immunosuppressants | 23 (89%) |
| Methotrexate | 9 (35%) |
| Azathioprine | 3 (12%) |
| Mycophenolate Mofetil | 10 (39%) |
| Cyclosporin | 1 (4%) |
| Antimalarials or GC only | 3 (12%) |
| **Reason for Anifrolumab prescription** | |
| Disease flare | 9 (35%) |
| Persistently active disease | 17 (65%) |
| **SLEDAI-2K**[1] | 8 (6-10) |
| **SLE-DAS**[1] | 6.7 (5.3-13.2) |
| **SLICC-DI >0** | 14 (54%) |
| **SLICC-DI**[1] | 2 (1-3) |
| **CLASI activity**[1] **/ damage**[1] (in patients with mucocutaneous involvement at baseline) | 12 (7-22) / 2 (0-8) |
| **Tender joints**[1] **/ Swollen joints**[1] (in patients with joint involvement at baseline) | 6 (3-10) / 2 (0-4) |
| **Physician Global Assessment**[1] **(0-3)** | 1 (1-1.6) |

[1] Median (IQR)

**Table 2. Disease activity indices and daily dosage of prednisone equivalent over time.**

| | **Baseline (T0) (N=26)** | **1 month (T4) (N=26)** | **3 months (T12) (N=24)** | **6 months (T24) (N=19)** | **9 months (T36) (N=13)** | ***p-value*** ° |
|---|---|---|---|---|---|---|
| **SLEDAI-2K** [median (IQR)] | 7.5 (6-10) | 6.0 (4-8) | 5.5 (2-7) | 2 (1-4) | 2 (0-2) | **T0 vs T4: 0.005**<br>**T0 vs T12: 0.003**<br>**T0 vs T24: <0.001** |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | **T0 vs T36: 0.002** |
| **SLE-DAS** [median (IQR)] | 6.7 (5.3-13.2) | 5.2 (4.0-6.8) | 3.1 (1.3-5.7) | 1.3 (1.1-3.0) | 1.1 (0.6-2.3) | **T0 vs T4: 0.005 T0 vs T12: 0.001 T0 vs T24: <0.001 T0 vs T36: 0.002** |
| **CLASI-A** * [median (IQR)] | 12 (7-22) | 4 (2-9) | 2 (1-5) | 0 (0-4) | 0 (0-0) | **T0 vs T4: <0.001 T0 vs T12: <0.001 T0 vs T24: <0.001 T0 vs T36: 0.012** |
| **Tj / Sj** § [median (IQR)] | 6 (3-10) / 2 (0-4) | 4 (2-10) / 1 (0-2) | 2 (0-8) / 0 (0-1) | 0 (0-3) / 0 (0-0) | 0 (0-1) / 0 (0-0) | **T0 vs T4: 0.026 / 0.017 T0 vs T12: n.s. / 0.021 T0 vs T24: n.s. / 0.043 T0 vs T36: 0.012 / 0.043** |
| **PGA (0-3)** [median (IQR)] | 1.0 (1.0-1.6) | 1.0 (0.6-1.0) | 0.5 (0.5-1.0) | 0.5 (0-1.0) | 0 (0-0.4) | **T0 vs T4: 0.001 T0 vs T12: <0.001 T0 vs T24: <0.001 T0 vs T36: 0.002** |
| **Daily GCs dosage (mg predn-eq)** [median (IQR)] | 7.3 (5-10) | 5 (5-8.1) | 5 (5-7.2) | 5 (2.5-7.5) | 5 (0.6-5.7) | **T0 vs T4: 0.045 T0 vs T12: 0.035 T0 vs T24: 0.049 T0 vs T36: n.s.** |

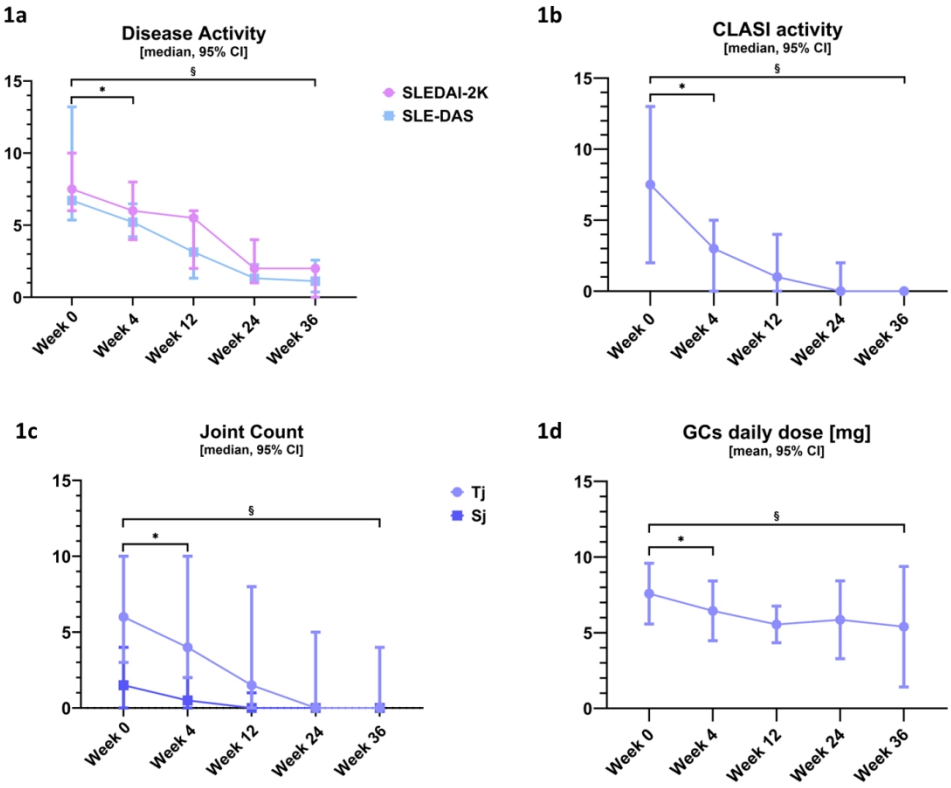
* only patients with mucocutaneous involvement at baseline

§ only patients with joint involvement at baseline

° paired samples Wilcoxon test

**Table 3. Adverse events.**

| | Total N of adverse events (N of patients in follow-up) | Infections (type) | Cardiovascular events | Other | Discontinuation (reason) / temporary suspension |
|---|---|---|---|---|---|
| **T4** | 6 (26) | 5 (3 upper respiratory tract infections, 1 urinary infection, 1 HSV) | 1 (paroxysmal supraventricular tachycardia) | 0 | 0 / 1 |
| **T12** | 7 (24) | 5 (2 urogenital tract infections, 1 gastroenteritis, 1 COVID-19, 1 Herpes Zoster) | 1 (pulmonary thromboembolism) | 1 (neutropenia) | 0 / 4 |
| **T24** | 5 (19) | 4 (1 urogenital tract infection, 1 gastroenteritis, 2 COVID-19) | 0 | 1 (fatigue) | 0 / 1 |
| **T36** | 5 (14) | 5 (2 upper respiratory tract infections, 1 urogenital tract infection, 1 cellulitis, 1 COVID-19) | 0 | 0 | 1 (recurrence of infections) / 1 |
| **T48** | 3 (7) | 3 (1 oral candidiasis, 1 upper respiratory tract infection, 1 COVID-19) | 0 | 0 | 0 / 1 |
| **T72** | 1 (1) | 1 (upper respiratory tract infection) | 0 | 0 | 0 / 0 |
| **TOTAL** | 27 | 23 | 2 | 2 | 1 / 8 |




Disease activity and GC-dosage over time

400x350mm (96 x 96 DPI)