Long-term continuation of methotrexate therapy in giant cell arteritis patients in clinical practice

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Received on September 22, 2016; accepted in revised form December 20, 2016.

Clin Exp Rheumatol 2017; 35 (Suppl. 103): S165-S170.

Key words: giant cell arteritis, methotrexate, corticosteroids, discontinuation, recurrence

Competing interests: none declared.

ABSTRACT

Objective. *To assess the long-term continuation of methotrexate (MTX) in a cohort of patients with giant cell arteritis (GCA) in daily clinical practice. Factors associated with its discontinuation rate were also investigated.*

Methods. *A longitudinal study from 1991–2014, was performed. GCA patients with MTX and followed up in a rheumatology outpatient clinic of Madrid during the study period were included. Primary outcome: discontinuation of MTX due to: adverse drug reactions (ADR moderate and severe); inefficacy; sustained clinical response; patient decision. Covariables: sociodemographic, clinical and therapy. Incidence rates (IR) of MTX discontinuation per 100 patient-years with their 95% confidence interval (CI) were estimated using survival techniques. Factors associated to specific discontinuation causes were analysed using Cox models.*

Results. *We included 108 patients (244 patient-years). The IR was 37.2 [30.3–45.7]. The IR due to ADR, severe ADR, sustained clinical response and inefficacy was 20.8 [15.8–27.4]; 5.7 [3.3–9.6]; 8.2 [5.3–12.7] and 2.8 [1.3–6.0] respectively. Regarding multivariate analysis, younger patients, baseline cardiovascular disease, taking more glucocorticoids and lower initial doses of MTX were associated to a higher discontinuation rate due to inefficacy. Factors influencing the suspension due to ADRs were: older age, baseline chronic obstructive pulmonary disease, higher baseline erythrocyte sedimentation rate, several specific clinical patterns at diagnosis, and higher maximum dose of MTX during the follow-up. In the final model for sustained clinical response older patients and more recurrences were independently associated to less discontinuation rate.*

Conclusion. *We provide further data of the potential safety of long-term MTX in the management of GCA. We have also found several factors influencing the continuation of MTX.*

Introduction

Giant cell arteritis (GCA) is a large and medium-sized blood vessel systemic vasculitis in the elderly, characterised by the granulomatous involvement of the aorta and its major branches (1). It is the most common systemic vasculitis in Western countries (2, 3).

Treatment with high doses of corticosteroids usually suppresses inflammatory activity dramatically, with subsequent tapering to a lower maintenance dose. However, adverse events are frequent, and flares are common (4, 5), being a major problem in the management of GCA in already frail patients. These issues have prompted investigations of alternative therapies for GCA.

Regarding immunosuppressant therapies, a small randomised study showed a steroid-sparing effect for azathioprine, but with toxicity that led to withdrawal in one third of the patients (6). Experience with cyclosporine has been scarce and their use is not advised for this population due to the inefficacy and high levels of toxicity (7). Concerning cyclophosphamide, a review of the literature has been published, concluding that it might be considered a sparing agent in some cases, especially when conventional immunosuppressive agents, such as methotrexate (MTX) or azathioprine, had failed (8).

Notably, several randomised, double-blind, placebo-controlled trials have studied the effect of combining low-dose MTX with glucocorticoids for treatment of GCA patients (9-11) with conflicting results. In a meta-analysis and in a systematic review developed after, they concluded that in GCA, adjunctive treatment with MTX lowers

the risk of relapse and reduces exposure to glucocorticoids (12, 13).
Finally, various biological agents have been also investigated, specifically infliximab and etanercept, showing inefficacy (14-16). Recently, it seems that patients with refractory GCA should be considered for tocilizumab therapy (17).
Based in clinical trials, MTX can be considered a feasible option in addition to standard-of-care treatment with corticosteroids for these patients, being recommended by EULAR (18), but there is a need to corroborate these results in real-life conditions. Therefore, our aim was to assess the long-term continuation and causes of MTX discontinuation in a cohort of patients with GCA in clinical practice. Furthermore, we analysed the influence of several demographic and disease-related variables, in the continuation of this drug.

Methods

Study design, patient sample, and data collection

An observational retrospective longitudinal study was performed. We selected patients attending the rheumatology outpatient clinic of the Hospital Clínico San Carlos (Madrid, Spain), with diagnosis (according to the 1990 American College of Rheumatology) (19) of GCA, aged ≥18 years which started treatment with MTX between January 1990 and December 2012, until the end of the study (September 2014).
Patient data in this project were obtained during routine clinical practice for 22 years with oral informed consent of patients to be treated in an assistance and research clinical service. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and was approved by the institutional ethics committee (CEIC Hospital Clínico San Carlos).
The study reviewed all the medical records to obtain the variables. Medical records were documented in writing for all patients seen from 1990 to December 2006. After that, data were registered in an Electronic Health Record (Medi-LOG, 2006) (20), used in our outpatient clinic, collected during routine consultation by rheumatologists.

Variables

Our primary endpoint was MTX discontinuation due to: a) adverse drug reaction (ADR) defined as an injury related to MTX during the study period (moderate [required discontinuation of the MTX]; or severe [patient discontinues the MTX and requires hospitalisation or dies as a result of the ADR]); b) inefficacy as rheumatologist criteria; c) patient decision; d) sustained clinical response as rheumatologist criteria; and e) other medical causes.
The following covariates were considered:
1. Sociodemographic: sex and age at diagnosis;
2. Baseline comorbid conditions (see Table I);
3. Temporal artery biopsy;
4. Clinical symptoms at diagnosis: headache, abnormal temporal artery in the exploration, cardiovascular symptoms, polymialgia rheumatica, visual disturbances (transient visual disturbances, diplopia, blurred vision, loss of vision), jaw claudication, large-vessel stenosis, thickening, tenderness, on temporal or occipital arteries, general symptoms (asthenia, weight loss, malaise, fever) and baseline erythrocyte sedimentation rate (ESR);
5. Treatment: a) defined as use of steroids starting dose and average dose in the first six months of diagnosis; b) starting with MTX at diagnosis (yes defined a in the first 8 weeks from the diagnosis); c) initial dose and maximum dose of MTX during the whole follow-up.
6. Number of GCA recurrences defined as after an objective improvement due to treatment with corticosteroids (absence of symptoms of GCA and normalisation of laboratory values) patient had a recurrence (presence again of symptoms or signs of arteritis with high ESR and increase in the dose of corticosteroids) during the study period.
7. Calendar time: time of diagnosis grouped by five year intervals.

Data analysis

A description of the sociodemographic and clinical characteristics of patients included and the causes of discontinuation were explored with frequency distribution and the mean and standard deviation or median and percentiles.
To explore discontinuation of the MTX regardless the cause and specifically related to ADR, inefficacy or sustained clinical response, we included all the patients with GCA and the time of exposure comprised the period from the starting of MTX until the occurrence of any of the following cut-off points: lost of follow-up, main outcome, or the end of the study. Kaplan-Meier curves were set to account for survival over time. Incidence rates (IR) of discontinuation were estimated by survival techniques (allowing for multiple-failure per patient), expressing the IR per 100 patient-years with their respective 95% confidence intervals (CI).
Cox bivariate analyses were made to asses the differences between sociodemographic, clinical and therapy covariates and the risk of discontinuation due to ADR, inefficacy or sustained clinical response. Cox multivariate regression analyses were run to compare continuation of MTX related to ADR, inefficacy or sustained clinical response. In multivariate analysis we also included age, sex, calendar time, and all variables found with a $p<0.2$ in the bivariate analysis. Results were expressed as hazard ratio (HR) and CI. Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. All analyses were performed in Stata v. 12 statistical software. A two-tailed p-value under 0.05 was considered to indicate statistical significance.

Results

108 patients were included in the study, whom began 137 different courses of MTX treatment. Table I includes a wide cohort description. Almost all patients, except one, were taking glucocorticoids at the beginning of study, with a median dose of 60 mg/day. 50% of the patients started with MTX in the first 28 days after diagnosis. 70% of the patients started with MTX within the first 8 weeks from the diagnosis, and in the rest, the median lag time until MTX was 5.7 [P25–75: 3.6–18] moths. The median dose was 10 mg / week, being the maximum dose 15 mg / week. The maximum time for patients on MTX was 8.4 years.

Table I. Baseline demographic and clinical characteristics of patients.

Patients (n)	108	
Courses of BA treatment	137	
Total follow up patient*year	244	
Women, n (%)	88	(81.5)
Mean age at diagnosis, mean ± SD7	6.6 ± 6.5	
Comorbilities, n (%)		
PAH	69	(63.9)
Hypercholesterolaemia	40	(37)
Cardiovascular disease	35	(32.4)
Congestive heart failure	13	(12)
Diabetes Mellitus	20	(18.5)
Polymyalgia rheumatica	17	(15.7)
Depression	15	(13.8)
Liver disease	3	(2.7)
Peptic ulcer disease	6	(5.5)
Renal insufficiency	6	(5.5)
Symptomatic vertebral fracture	9	(8.3)
Cancer	7	(6.4)
COPD	11	(10.2)
ESR (mm/h), median [p25-p75]	85	[63-104]
Temporal positive artery biopsy, n (%)	63	(58)
Lag time in months from diagnosis to MTX, median [p25-p75]	0.95	[0.12-2.9]
MTX dose (mg/week) at diagnosis, mean ± SD	9.85 ± 1	
Aspirin at diagnosis, n (%)	39	(36)
Statins at diagnosis, n (%)	23	(21)
Glucocorticoids, n (%)	107	(99)
Glucocorticoids dose (mg/día) at diagnosis, mean ± SD	50.7 ± 16	
Clinical symptoms:		
Headache	94	(87)
General symptoms	68	(62.9)
Polymyalgia rheumatica	61	(56.4)
Jaw claudication	43	(40.2)
Abnormal temporal artery	41	(37.9)
Visual disturbances	38	(35.2)
Peripheral joint pain	15	(13.8)
Glucocorticoids at 6 months, mean ± SD	22.5 ± 8.5	

BA: biologic agents; SD: standard deviation; COPD: chronic obstructive pulmonary disease

Table II. Incidence rate (IR) of MTX discontinuation by gender, cause, calendar and causes.

	Patients*year	Events (n)	IR	95% CI
Total	244	91	37.26	[30.3 – 45.7]
Gender				
Women	212	70	32.9	[26.1 – 41.6]
Men	32	21	66.1	[43.1 – 101.3]
Age categories				
60–75	99	37	37.2	[27 – 51.4]
75–85	130	41	31.4	[23 – 42.7]
>85	15	13	88	[51.1 – 151.6]
Calendar time				
1990 – 1995	13	10	78	[41.9 – 144.9]
1996 – 2000	17	12	71	[40.5 – 12.5.6]
2001 – 2005	57	23	40.3	[26.7 – 60.5]
2006 – 2010	119	35	29.3	[21.05 – 40.8]
>2011	38	11	28.9	[16 – 52.2]
Discontinuation causes	244			
ADR		**51**	20.8	[15.8 – 27.4]
Moderate		37	15.1	[10.9 – 20.9]
Severe		4	1.6	[0.6-4.36]
ADR Death		14	5.7	[3.4-9.6]
ADR Infections		31	12.6	[8.9-18]
Sustained clinical response		**20**	8.2	[5.3 – 12.7]
Inefficacy		**7**	2.8	[1.3 – 6.0]
Patient decision		**7**	2.8	[1.3 – 6.0]
Other medical causes		**7**	2.8	[1.3 – 6.0]

Regarding other therapies, 17.5% of the patients (n=19) had taken other disease-modifying anti-rheumatic drugs (DMARDs) (n=31) including azathioprine (n=15; 48%), cyclophosphamide (n=7; 22%), antimalarials (n=3; 9%), infliximab (n=4), tocilizumab (n=1)) and cyclosporine (n=1). Most of them (n=28) after MTX discontinuation, one of them before MTX and two of them during the course of MTX. Regarding the latest, one patient was taking antimalarials combined with MTX for almost a year, and the patient discontinued antimalarials due to digestive intolerance and continued with MTX. The other patient was taking combined MTX with tocilizumab with good tolerance for almost a year until the end of the study.

51% of patients had relapses during follow-up, the median (interquartile range) number of relapses were 1 (0–2), 50% occurring during the first year. Specifically related to the first one, the median lag time to relapse was 0.5 [0.4–1.5] years.

We found a total of 91 MTX discontinuations during follow-up (66.4%). 26% of discontinuations were temporary (minimum 15 days and maximum 24 months) mainly related to mild infections (upper respiratory tract infections, gastroenteritis, and herpes zoster), 12.5% due to reversible analytic alterations; 12.5% clinical improvement and the remaining 8.3% due to patient decision.

The IR of discontinuation (Table II), regardless the cause, was estimated in 37.2 per 100 patient-years. The median survival rate was 1.7 [1.3–2.2] years, and the retention rate was 77% at 6 months, 68 % at 12 months, 47% at 2 years, 26% at 3 years, 18% at 5 years and 7% at 8 years.

From all the discontinuations, 51 (56%) were due to ADRs. Of them, 37 (73%) were moderate and 14 (27%) were severe, including 4 deaths directly related to MTX. The most frequent cause for ADRs (61%) were infections, being 54% and 78% of the total causes of moderate and severe ADRs, respectively (Fig. 1). Infections in moderate ADRs were mainly related to the upper respiratory tract (60%); followed by herpes zoster (15%). In severe ADRs, infections (IR: 4.5[2.4–8.1], n=11) were due to pneumonias (73%), followed by one sepsis, one gastroenteritis and one cholecystitis. Finally, 75% (n=3) of the deaths were as a result of infections and the other one due to an abdominal cancer.

The second most frequent cause of MTX discontinuation was sustained clinical response (n=20, 15%). Inefficacy accounted for less than 6% (n=7) of the discontinuations (Fig. 2).

Factors associated with discontinuation (Table III)

• *Inefficacy*

In the multivariate analysis, younger patients, with baseline cardiovascular disease, with higher mean dose of glucoglucocorticoids and with lower starting dose of MTX were the variables in-

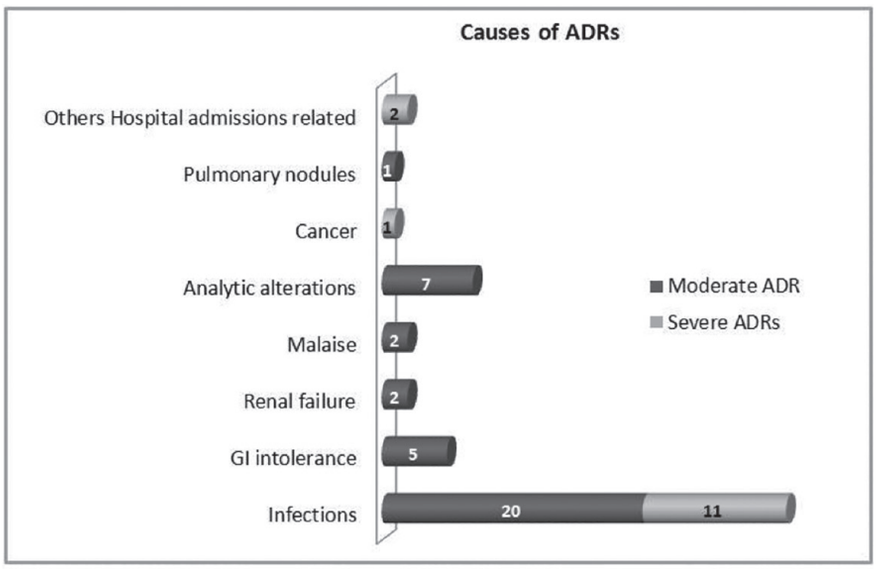

Fig. 1. Causes of moderate and severe ADRs.

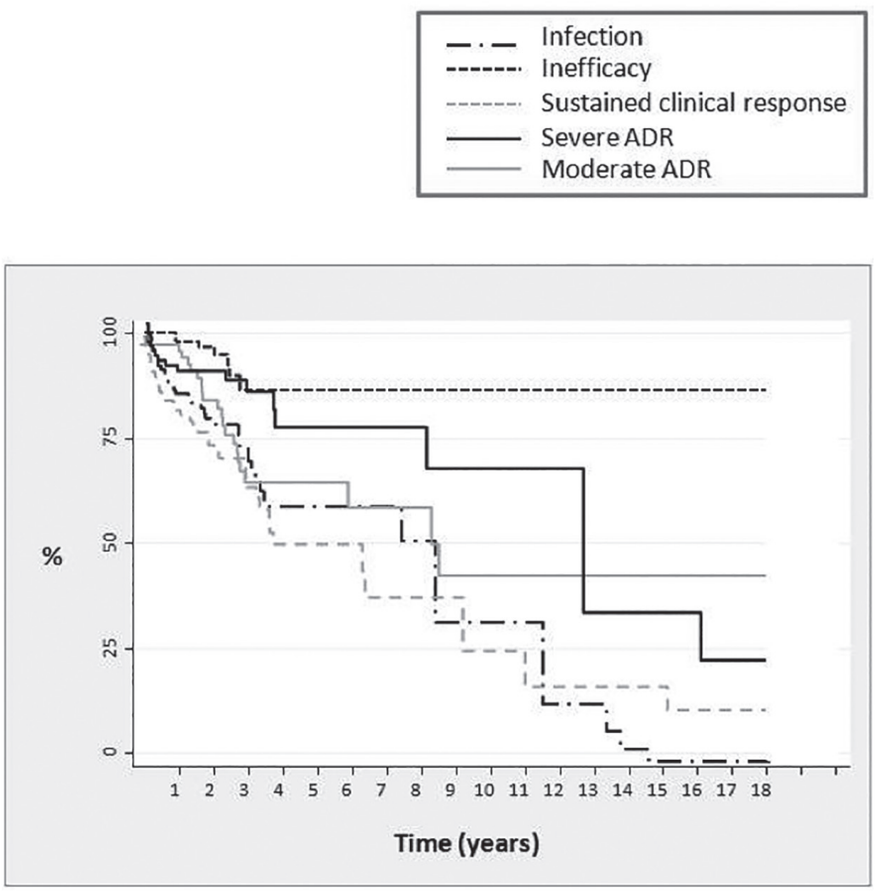

Fig. 2. Kaplan-Meier failure estimate curves, by the main causes of MTX discontinuation.

dependently associated with higher risk of discontinuation due to inefficacy.

•*Adverse drug reactions*

In the multivariate analysis, older age, baseline Chronic obstructive pulmonary disease (COPD), higher baseline ESR, several specific clinical presentation, and higher maximum dose of MTX during the follow up, remained in the final model with statistical significance. Glucocorticoids also achieved a trend whereas lag time until starting with MTX did not have any influence.

Regarding severe ADRs, the final model included older age (HR: 1.09[0.98–1.21]; p=0.09); presence of baseline COPD (HR: 9.7[2.4–39.3]; p=0.001); positive arterial biopsy (HR: 0.26 [0.09–0.7]; p=0.01); clinical presentation with cardiovascular disease (HR: 10.6[1.8–62.8]; p=0.009). Nevertheless, mean dose of glucocorticoids during the first 6 months was not significant (HR: 1.01[0.9–1.1]; p=0.6).

• *Sustained clinical response*

In the final model, older patients, and higher number of recurrences were independently associated with a lower risk of discontinuation due to sustained clinical response. Starting with MTX at diagnosis (p=0.4) was not included in the model.

Discussion

To our knowledge, this is the first study that shows the long term continuation of metothrexate in GCA prescribed in daily clinical practice. While the incidence of ADRs is elevated, most of them were reversible without severe clinical impact. Therefore, it seems that MTX is a safe drug in the treatment of GCA. Moreover, we also want to highlight the lower incidence of discontinuations due to inefficiency compared to the discontinuations due to sustained clinical response. Finally, we have found several sociodemographic and clinical factors that can modify the continuation of MTX.

These patients are a part of one cohort of GCA followed-up in daily clinical practice, including all patients attended and followed up from the early nineties until 2014 in our Health Area, independently of the therapy received. For the purpose of this study, we have selected all on MTX therapy, ideal to assess the survival of this drug in the long term. Most of our patients were women with a mean age at diagnosis of 76.6 years with the typical clinical presentation of this disease (4, 21). From those patients with temporal artery biopsy, 64% were positive and almost 30% negative as in other series (22, 23). Regarding the treatment, the most common start-

Table III. Multivariate Cox regression analysis, adjusted by age, gender, calendar time and other confounding factors.

	Adverse drug reaction			Sustained clinical response			Inefficacy		
	HR	95% IC	*p*	HR	95% IC	*p*	HR	95% IC	*p*
Gender, men	0.3	0.08-1.01	0.07	0.99	0.29-3.3	0.9	0.56	0.12-2.5	0.4
Age at diagnosis	1.06	1.01-1.3	0.03	0.91	0.82-0.99	0.03	0.86	0.7-0.96	0.013
Calendar time	0.98	0.7-1.3	0.8	0.40	0.23-0.73	0.003	0.19	0.04-0.9	0.04
COPD	2.74	0.99-7.1	0.05	-	-	-	-	-	-
ESR	1.02	1.01-1.03	0.001	-	-	-	-	-	-
Cardiovascular disease	-	-	-	-	-	-	16.5	1.6-165	0.017
Mean Glucocorticoids dose at 6 months	1.03	0.99-1.07	0.07	0.95	0.89-1.01	0.1	1.25	1.04-1.5	0.014
Maximum MTX dose	0.75	0.67-0.83	0.000	-	-	-	-	-	-
Initial MTX dose	-	-	-	-	-	-	0.31	0.17-0.55	0.000
Visual disturbances	3.29	1.5-7.0	0.002	-	-	-	18.9	0.99-361	0.05
Jaw claudication	2.57	1.23-5.37	0.012	-	-	-	-	-	-
Cardiovascular clinic	8.3	3.8-17.8	0.000	-	-	-	-	-	-
Number of recurrences	-	-	-	0.56	0.36-0.84	0.006	-	-	-

ing dosage over the study period was 60 mg of prednisone (18) per day plus MTX 10 mg every week.

The discontinuation rate of MTX seems to be high, compared to other diseases, such as rheumatoid arthritis (RA), being around three times lower studies (24-26). But we have to take into account that GCA patients are elderly, with concomitant high dose of glucocorticoids (4) and with comorbidity that might influence the development of ADRs. In spite of this, most of them were not severe with complete resolution after several weeks. In accordance with other studies, ADRs were related to infections and mainly of the respiratory tract (27, 28). We have found lower mortality rates than other published studies (29-31), while we have evaluated the mortality rate directly related to MTX therapy.

An interesting finding is that the second most frequent cause of MTX discontinuation was due to sustained clinical response. Patients remained with MTX until at least one more year on this situation, and most of the discontinuations related to this cause occurred after the second and third year of therapy. Inefficacy accounted for less than 6% of the discontinuations, and always was in the first three years of therapy.

Our study also helps to identify associated factors that may modify the survival of MTX. Regarding ADR discontinuations, our results corroborate that older age and cumulative doses of glucocorticoids increase the risk of ADRs (4). We have also shown that the severity of the disease presentation, might imply a higher risk of discontinuation due to ADRs. Moreover, when we analysed specifically severe ADRs, older age, the presence of baseline COPD, and a clinical presentation with cardiovascular disease, were associated with a higher hazard of discontinuation. As a consequence, a close monitoring should be considered for these patients.

Another finding was the lower risk of the maximum dose of MTX reached during the follow-up to discontinuation due to ADRs. This makes sense if we know that MTX is a corticosteroid sparing drug and also because the maximum level of MTX never reached above 15 mg. This dose could be considered safe, if we take into account that the optimal dose in other rheumatic diseases such as RA is higher.

Finally, in relation to inefficacy, younger patients, with baseline comorbidity (specifically cardiovascular disease), with a higher average dose of glucocorticoids and lower starting dose of MTX, were independently associated with a higher risk of discontinuation due to this cause.

Our study has several limitations. First, given the retrospective nature of the design, data obtained relies on documentation available in the medical records. Another limitation is the low number of patients included, but we have to take into account the low prevalence of this disease. However, one of the greatest strengths of this study is the long-term follow up of patients and in clinical practice, adjusted for multiple confounders.

In conclusion, our cohort provides further evidence of the potential safety of MTX in the management of patients with GCA. Moreover we have seen that there are several modifiable and non-modifiable factors that might influence the continuation of MTX and thus its safety. We think the point should be to start with MTX at least 7.5–10 mg in early stages of disease, with recommended dosages of glucocorticoids. This could help to decrease glucocorticoids quickly, thus avoiding the risk of ADRs, inefficacy and increasing the likelihood of improvement. It is also important to take into account that we are treating older patients with comorbility, thus close monitoring should be mandatory to avoid ADRs.

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