Giant cell arteritis: intensity of the initial systemic inflammatory response and the course of the disease

G. Nesher[1], R. Nesher[2], M. Mates[3], M. Sonnenblick[3], G.S. Breuer[3]

[1]Shaare-Zedek Medical Center and the Hebrew University Medical School, Jerusalem Israel, and St. Louis University School of Medicine, St. Louis, Missouri, USA; [2]Meir Medical Center, Kfar-Saba, and the Tel-Aviv University Sackler Medical School, Tel Aviv, Israel; [3]Shaare-Zedek Medical Center, Jerusalem, and the Ben-Gurion University Medical School, Beer-Sheba, Israel.

Gideon Nesher, MD, Associate Professor; Ronit Nesher, MD, Lecturer; Michal Mates, MD, Lecturer; Moshe Sonnenblick, MD, Associate Professor; Gabriel S. Breuer, MD, Lecturer.

Please address correspondence to: Gideon Nesher MD, Department of Internal Medicine, Shaare-Zedek Medical Center, P.O. Box 3235, Jerusalem 91031, Israel.
E-mail: nesher@inter.net.il

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ABSTRACT

Objective. *Giant cell arteritis (GCA) has a variable course. We assessed whether intensity of initial systemic inflammatory response (ISIR) can predict the course of GCA.*

Methods. *Charts of 130 GCA patients were reviewed. ISIR intensity at presentation was determined by 5 parameters of inflammation: sedimentation rate >100mm/h, thrombocytosis >400,000/μl, hemoglobin <11g/dl, leukocytosis >11000/μl, and fever >37.5°C. Patients were divided into 3 groups according to ISIR intensity: strong (4-5 parameters present, n=24), moderate (2-3 parameters, n=55) and weak ISIR (0-1 parameter, n=51).*

Results. *There were no significant differences between these groups regarding mean age, female:male ratio and the initial prednisone dose. At 1 year, 75% of patients in the strong ISIR group required >5mg/d of prednisone, compared to 54% and 37% of patients with moderate or weak ISIR, respectively (p=0.015). Disease flares were more common in patients with strong ISIR during a 3-year period, compared to patients with moderate or weak ISIR (77%, 67% and 43%, respectively, p=0.013). Only 33% of patients with strong ISIR were able to discontinue steroids after 3 years, compared to 49% and 77% of patients with moderate and weak ISIR, respectively (p=0.003).*

Conclusions. *GCA Patients with strong ISIR have prolonged disease course with more flares, requiring higher steroid doses. ISIR intensity should be taken into consideration when planning studies evaluating potential steroid-sparing agents, as response to treatment may vary in patients with different ISIR intensities.*

Introduction

Patients with giant cell arteritis (GCA) have variable courses of their disease. In some patients it is possible to discontinue steroid therapy within 2-3 years without recurrence of the disease, while others need prolonged treatment (1-3). Patients may experience disease flares during the course of GCA, while others do not (1-3). The reasons for this varied course and outcome are not clear.

In recent years attention has been drawn to the initial systemic inflammatory response (ISIR) in GCA (4-10). The ISIR includes clinical manifestations such as fever, anorexia and weight loss, and laboratory abnormalities such as markedly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), anemia, thrombocytosis and leukocytosis. Several groups of researchers reported that strong intensity of ISIR or some of its individual parameters (such as fever and anemia) are associated with decreased rate of GCA-associated cranial ischemic complications at the onset of the disease (4, 6, 9-11). Regarding the course of GCA following treatment, one study reported that GCA without localizing signs ("masked" GCA) was associated with strong ISIR and a benign, short-term course (5). On the other hand, another study reported that strong ISIR was associated with higher steroid requirements, more flares and longer duration of therapy (7).

In this study we assessed whether the intensity of ISIR, based on 5 clinical and laboratory parameters, can predict the course of GCA, in regard to duration of therapy, corticosteroid dosage requirements, disease flares and outcome.

Patients and methods

Charts of patients with GCA diagnosed between 1980-2004 in one medical center were reviewed. In 116 patients the diagnosis was biopsy-proven. Fourteen biopsy-negative cases were included as they met the 1990 American College of Rheumatology (ACR)

criteria for GCA classification (12), in addition to rapid response of their symptoms to steroid therapy. Initial and one-year clinical and laboratory data were available for all 130 patients and 3-year follow-up data were available for 113 patients.

Admission data included the patient's age, gender, symptoms at presentation and their duration, significant findings on physical examination and results of laboratory tests. Follow-up data included the dose of prednisone and development of disease flares or complications. Disease flares were defined as signs or symptoms related to GCA, occurring during therapy or following cessation of therapy, and resulting in increasing the dose of prednisone or resuming corticosteroid therapy. Increasing ESR or CRP, when not associated with GCA-related signs or symptoms, was not considered GCA exacerbation. Patients were considered as having sustained remission off treatment when corticosteroids were discontinued without any disease relapse during the following 6 months.

ISIR intensity was determined by 5 parameters of inflammation: ESR >100 mm/h, thrombocytosis (platelet count > 400,000/μl), anemia (hemoglobin <11 g/dl), leukocytosis (leukocytes >11000/μl), and fever (>37.5°C). Patients were divided into 3 groups according to the intensity of ISIR, in advance of analyzing the data. Patients with strong ISIR had 4-5 parameters present, patients with moderate ISIR had 2-3 parameters, and patients with weak ISIR had 0-1 parameter present.

Significance of differences among the groups was assessed by chi-square analysis of contingency tables for categorical variables. Continuous variables with normal distribution were evaluated by one-way analysis of variance, otherwise the nonparametric Kruskal-Wallis test was applied.

Table I. Characteristics of 130 GCA patients, divided into 3 groups according to their intensity of systemic inflammatory response (ISIR)*.

	Strong ISIR	Moderate ISIR	Weak ISIR	*p*
n	24	55	51	
Mean age	71.7 ± 8.5	74.1 ± 7.7	72.2 ± 7.7	0.328
Females	17 (71%)	33 (60%)	34 (67%)	0.603
Eye or neurological symptoms (transient or irreversible) at presentation	4 (17%)	20 (36%)	22 (43%)	0.08
PMR at presentation	16 (67%)	17 (31%)	19 (37%)	0.01
Positive biopsy	23 (96%)	47 (85%)	46 (90%)	0.376
Mean initial dose of prednisone (mg/d)	53.3±10.9	55.6 ± 15.5	56.5 ± 16.8	0.701
ESR >100 mm/h	24 (100%)	40 (73%)	17 (33%)	<0.001
Platelets >400,000/μl	23 (96%)	40 (73%)	19 (37%)	<0.001
Hemoglobin <11g/dl	22 (92%)	22 (40%)	2 (4%)	<0.001
Leukocytes > 11000/μl	19 (79%)	22 (40%)	6 (12%)	<0.001
Fever >37.5° C	20 (83%)	16 (29%)	4 (8%)	<0.001

*ISIR intensity was determined by 5 parameters of inflammation: ESR >100 mm/h, thrombocytosis >400,000/μl, hemoglobin <11 g/dl, leukocytosis >11000/μl, and fever >37.5° C. Patients with strong ISIR had 4-5 parameters present, patients with moderate ISIR had 2-3, and patients with weak ISIR had 0-1.

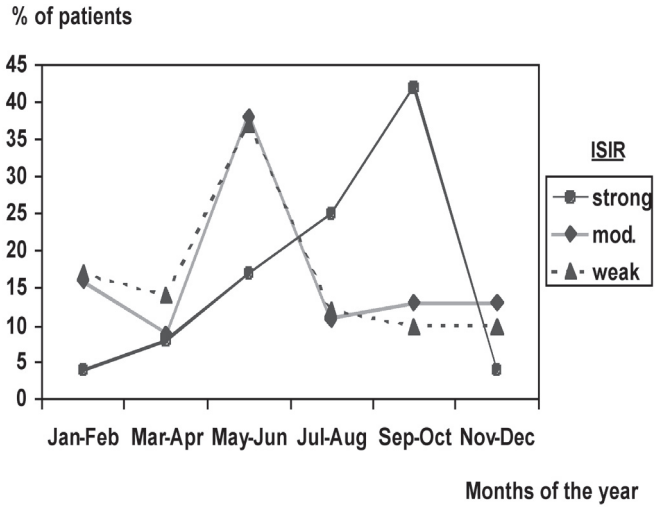

Fig. 1. Rates of GCA presentation throughout the months of the year in relation to the intensity of the initial systemic inflammatory response (ISIR).

Results

Strong ISIR was present in 24 patients, 55 had moderate ISIR and 51 had weak ISIR. There were no significant differences between these groups regarding the mean age, female:male ratio, the positive biopsy rate and the initial dose of prednisone (Table I). Polymyalgia rheumatica (PMR) was twice as common in the strong ISIR group compared to the other groups (p=0.01). Transient or irreversible neuro-ophthalmic manifestations were less common at presentation in the strong ISIR group, with borderline significance (p=0.08).

Data on the duration of GCA-related symptoms prior to diagnosis was available in 127 cases. Accordingly, the month of initial GCA symptoms was determined for each patient. For patients with strong ISIR the peak occurrence was in the months of September-October, while for the other patients the incidence peaked in the months of May-June (Fig. 1).

Twelve patients (9%) died during the first year of follow-up. Mortality rate was slightly higher in the strong ISIR group, but this did not reach statistical significance. Follow-up data at one year were available for the remainder 118 patients (Table II). Disease flares occurred during the first year in 55 patients (42%). Disease flares were less common among patients with weak ISIR (p=0.057).

At the end of the first year 75% of the patients in the strong ISIR group required >5mg/d of prednisone to keep their disease in remission. This proportion was significantly higher than in patients with moderate or weak ISIR (54% and 37%, respectively, p=0.015).

Table II. Outcome of GCA after one year of follow up in relation to the intensity of the initial systemic inflammatory response (ISIR).

	Strong ISIR	Moderate ISIR	Weak ISIR	*p*
Initial cohort (n)	24	55	51	
1-year mortality	4 (17%)	3 (5%)	5 (10%)	0.281
Patients with 1 year of follow-up (n)	20	52	46	
Patients with disease flares*	12 (50%)	28 (51%)	15 (29%)	0.057
Patients using >5mg/d prednisone at the end of 1 year**	15 (75%)	28 (54%)	17 (37%)	0.015

*% of initial cohort
**% of patients with 1 year of follow-up

Table III. Outcome of GCA after 3 years of follow up, in relation to the intensity of the initial systemic inflammatory response (ISIR).

	Strong ISIR	Moderate ISIR	Weak ISIR	*p*
Initial cohort (n)	24	55	51	
Patients lost to follow-up	2	10	5	0.330
3-year mortality*	4 (18%)	6 (13%)	7 (15%)	0.872
Patients who completed 3 years follow-up (on or off treatment)	18	39	39	
Patients with disease flares*	17 (77%)	30 (67%)	20 (43%)	0.013
Patients with new or recurrent loss of vision*	0	3 (7%)	2 (4%)	0.484
Mean dose of prednisone (in mg/d) at the end of 3 years	5.2 ± 3.2	4.3 ± 3.8	3.7 ± 5.3	0.003
Patients with sustained remission off steroids**	6 (33%)	19 (49%)	30 (77%)	0.003

*% of initial cohort less patients who were lost to follow-up
**% of patients who completed 3 years of follow-up

Table IV. Features of disease flares in GCA patients with strong, moderate or weak intensity of the initial systemic inflammatory response (ISIR), during a 3-year follow-up period.

	Strong ISIR	Moderate ISIR	Weak ISIR	*p*
Number of patients with disease flares	17	30	20	
Number of disease flares	22	37	28	
Headache, n (%)	11 (50)	21 (54)	10 (36)	0.24
Polymyalgia rheumatica, n (%)	10 (45)	18 (49)	16 (57)	0.68
Systemic symptoms (fever, anorexia), n (%)	4 (18)	4 (11)	2 (7)	0.47
Eye or neurological symptoms (transient or irreversible), n (%)	3 (18)	5 (13)	4 (14)	0.99
≥2 symptoms together as a sign of flare, n (%)	4 (18)	10 (27)	4 (14)	0.43
Elevated ESR or CRP, n (%)	20 (91)	33 (89)	26 (93)	0.88

By the end of the third year of follow up, data regarding 17 of the patients were not available. Data on the remaining patients are elaborated in Table III. The 3-year mortality rate was similar among the 3 groups of patients. Disease flares were more common among patients with strong ISIR during this 3-year period, compared to patients with moderate or weak ISIR (77%, 67% and 43%, respectively, p=0.013). Features of the disease flares were not significantly different among the three groups of patients (Table IV). The most common manifestations of disease flares were PMR and headaches. Patients with weak ISIR tended to have more PMR and less headaches and systemic symptoms compared to the other groups, however these trends did not reach statistical significance.

The mean daily dosage of prednisone at the end of 3 years was slightly but significantly higher in the strong ISIR group compared to the other groups (Table III). Only 33% of patients with strong ISIR were able to discontinue corticosteroid therapy by the end of 3 years. This rate was significantly lower compared to patients with moderate or weak ISIR (49% and 77%, respectively, p=0.003). Time to completion of corticosteroid therapy was shorter in the weak ISIR group compared to the combined moderate-strong group (p<0.001). Corticosteroid therapy was completed in 6 months in 4 of the 24 patients in this group, without recurrence of the disease. No patient in the other groups was able to discontinue therapy in less than one year.

New or recurrent irreversible vision loss occurred in 5 patients (Table III). None of these patients was in the strong ISIR group, however no conclusions can be drawn based on such small numbers. Considering all transient and irreversible neuro-ophthalmic manifestations, no difference was observed among the three groups of patients during the 3-year follow-up (Table IV).

Discussion

The intensity of ISIR may predict some aspects along the course of GCA. Patients with weak ISIR required lower doses of prednisone to keep their disease in remission, had less disease relapses and needed shorter periods of corticosteroid therapy.

Our data are in complete agreement with data reported by Hernandez-Rodriguez *et al*. (7). This group of researchers retrospectively reviewed 75 GCA patients and used 4 parameters of inflammation (ESR ≥85 mm/h, hemoglobin <11g/dl, weight loss and fever), to divide their patients into two groups (strong and weak ISIR). Patients with strong ISIR experienced more flares (77% compared to 55% of the weak ISIR group). Their median time to reach a maintenance dose of less than10 mg/d of prednisone was longer (62 weeks compared to 40 weeks in patients with weak ISIR). Only 17% of patients with strong ISIR, compared to 42% of patients with weak ISIR, completed steroid therapy by the end of their follow-up period (mean follow up periods were 40 and 31 months, respectively).

Other investigators described an association between initial ESR and the course of GCA or PMR. Hachulla and coworkers reported an association between the initial ESR and the relapse rate during corticosteroid tapering (13). Weyand *et al*. found that PMR patients with low ESR had disease flares rarely, and required short periods of steroid therapy (14). Gonzalez-Gay *et al*. reported that GCA patients with PMR and severe inflammatory response at the time of diagnosis, were more likely to develop aortic aneurysms at a later stage (15). In contrast to those reports, Liozon *et al*. reported that patients with "masked" GCA, presenting with systemic symptoms (most of them with fever, high ESR and low hemoglobin) without localizing cranial signs or symptoms, had excellent response to steroids and benign short-term outcome (5). The mean dose of prednisone at 6 months was similar to other GCA patients. It is possible that those patients with "systemic-onset" GCA without localizing symptoms comprise a subgroup of GCA, which differs from the subgroup of GCA patients with systemic symptoms accompanying localizing symptoms. It seems that this systemic-onset subgroup runs a milder course.

There are ample data showing that strong ISIR, or several individual inflammatory parameters such as fever and anemia are negatively associated with ischemic complications such as vision loss or stroke, occurring at the time of disease presentation (4, 6, 9-11). Data on ischemic complications occurring later in the course of GCA are scarce (6). In our cohort, neuro-ophthalmic manifestations at the time of presentation were indeed less common in the strong ISIR group. During the 3-year follow-up five patients developed vision loss, none of them had strong ISIR. However no difference was observed among the 3 ISIR groups when all ischemic neurological and ophthalmic manifestations were considered (Table IV). Those late-occurring ischemic complications do not seem to be associated with ISIR intensity, but the number of such patients in this cohort was too small to draw any significant conclusions regarding a possible association between intensity of ISIR and late-occurring vision loss or ischemic neurological events.

The reasons for this dual effect of the strong ISIR, negative association with ischemic complications at presentation of the disease on one hand and protracted course of the disease on the other hand, are not clear. Patients with strong ISIR have higher levels of circulating tumor necrosis factor (TNF) α and interleukin (IL)-6, and increased tissue production in the inflamed arteries of IL-6, IL-1β and TNF-α (7, 8). It is possible that some of these cytokines contribute to the negative association with ischemic complications (possibly IL-6), while others contribute to the protracted course with higher steroid requirements (possibly TNF-α, IL-1, and also IL-6) (7, 8, 14, 16). It is also not clear whether patients with strong ISIR have stronger inflammation in their arteries compared to patients with weak ISIR, or they just react with stronger acute phase response to the same level of vascular inflammation. It would be difficult to have a definite answer, but a recent retrospective study on GCA patients found an association between histological subtypes and disease flares and complications (17). Taken together with our observation, it may suggest that the intensity of the acute phase reaction reflects the intensity of the vascular inflammation.

Occurrence of strong ISIR peaked in autumn, while occurrence of weak and moderate ISIR peaked in spring and early summer (Fig. 1). This pattern was consistent over the years. Different seasonal patterns of GCA occurrence were reported by several authors, but no relationship to clinical features at presentation was described. Petrusdottir *et al*. reported peak incidence of biopsy-positive GCA in late winter and autumn (18), while Smeeth *et al*. found higher rates during late spring and early summer (19). Other epidemiological studies did not find any seasonal effect on the onset of GCA (20, 21). In a recent 25-year analysis of the entire population of GCA patients in Jerusalem (n=206) (22), we observed two peaks of occurrence: a major peak in May-June, and a smaller peak in October, probably corresponding to the weak-moderate and strong ISIR groups, respectively. The differential seasonal pattern observed in patients with weak-moderate and strong ISIR may be suggestive of different environmental factors associated with these varied presenting manifestations and disease course.

In our patient population PMR was more common in patients with strong ISIR. Such an association was not found previously, although GCA patients with PMR and severe ISIR were more likely to develop aortic aneurysms at a later stage (15). Hernandez-Rodriguez *et al*. (7) found similar rates of PMR in GCA patients with strong and weak ISIR (46% and 40%, respectively). Gonzalez-Gay *et al*. also found similar rates of PMR in GCA patients with and without fever (9), and suggested that PMR in biopsy proven GCA does not constitute a different subset (23).

There is always some uncertainty concerning the validity of results of retrospective studies. Hernandez-Rodriguez *et al*. (7) already showed an association between ISIR intensity based on 4 parameters, and some features of GCA disease course. In our study we used different parameters of ISIR intensity, on a larger cohort. Reaching similar conclusions by the two different studies on two entirely different populations increases the confidence in the validity of these results.

This observation may affect the planned course of treatment in GCA patients. On one hand, those with strong ISIR are likely to have a protracted course of steroid therapy, presumably with increased risk of steroid-related side effects. Awareness of this possibility is important, and the use of preventive measures should be more strongly considered. On the other hand, patients with weak ISIR are likely to have a milder course, and a shorter duration of corticosteroid therapy may be attempted. Our observation may also affect the planning of studies evaluating potential steroid-sparing agents for the treatment of GCA. The ISIR intensity should be taken into consideration when planning and conducting such studies, as response to treatment varies in patients with different ISIR intensities.

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