Poor performance of IgG4-related disease responder index in children

Sirs,

Immunoglobulin G4-related disease (IgG4-RD) is a systemic and fibroinflammatory condition which is very rare in children (1). Our knowledge is mainly based on adult experience. The risk of severe organ damage due to fibrosis makes IgG4-RD an entity that requires careful monitoring (2). In adults, an IgG4-RD responder index (IgG4-RD RI) was developed to assess the disease activity and damage, and to evaluate the effectiveness of treatment (3). Physicians give a score from 0-3 (0: unaffected or resolved, 1: improved but persistent, 2: new or recurrence while not receiving treatment, or unchanged, 3: worse or new lesion despite treatment) for each organ system affected. Whether the disease is symptomatic, requires urgent treatment, and the presence of damage are also evaluated (3). However, the responder index has not been tested in childhood cases. We have tested this scoring system in our cohort of paediatric patients with IgG4-RD (4). Patients followed up between June 2014 and September 2020 were included in the study. Demographic variables, IgG4-RD RI, as well as physician, and patient global assessment (GA) were evaluated retrospectively at diagnosis, at sixth months, and then annually. The correlation between these scores was evaluated using Spearman's rank correlation coefficient.

A total of eight patients (four female) with a median age of 13.4 (IQR 9.5-15.0) years were included. IgG4-related ophthalmic disease was the most common clinical presentation observed in six patients (75%). One of the remaining two patients had IgG4-related lymphadenopathy and the other had IgG4-related sialadenitis and lymphadenopathy of several lymph nodes accompanied by pancreatitis, ulcerative colitis, and pulmonary manifestations. The median follow-up time was 3.6 years (min-max: 0-7 years).

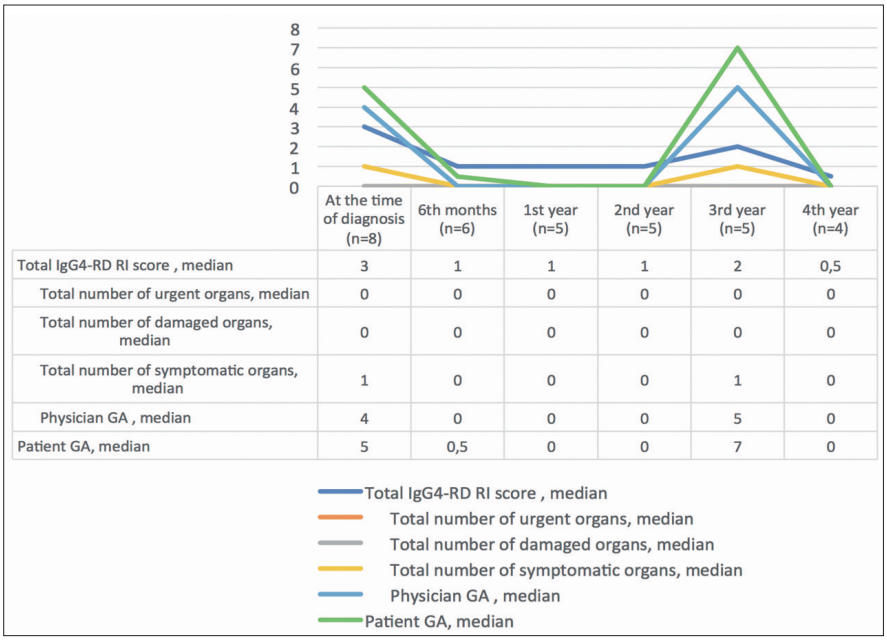
No correlation was found between the IgG4-RD RI score and patient and physician GA scores at diagnosis and follow-up. However, there was a strong correlation between patient and physician GA scores both at the diagnosis and follow-up (p=0.001, r=0.924 at the diagnosis; p<0.001, r=0.984 at the 6-month visit, p=0.029, r=0.917 at the 3-year visit, and p<0.001, r=1.0 in the last visit).

None of the patients developed an urgent medical condition (Fig. 1). Organ damage occurred in a patient with orbital involvement after five years of diagnosis. Two patients with orbital involvement had a relapse. One had a relapse on the 27 months of treatment while the other had a relapse occurred 38 months after diagnosis.

The disease responder index plays a crucial role in the monitoring of the disease and evaluating treatment response. However, paediatric patients mainly have single organ involvements without the need for urgent intervention. The median number of involved organs in our paediatric group was low compared to adult cohort of our group (1 *vs.* 2, p=0.02) (4, 5). An individual active organ involvement can cause very severe clinical disturbance although not described as an ''urgent disease''. Patients and physicians may assign a high score for the assessment of the disease, which might have caused the discordance between the IgG4-RD RI and patient and physician GA. Although a high correlation was reported between IgG4-RD RI and physician's GA in adults, assessment and scoring of main symptoms separately for each organ may be more appropriate to accurately assess the severity. Lanzillotta *et al*. also stated that high scores would not correspond to different treatments or outcomes (6).

Different serum IgG4 levels were reported to be associated with different clinical features and treatment responses in adults (7). Another consideration is whether IgG4 levels should be a part of this responder index in children? We would suggest against it since single organ involvement dominates the picture in paediatric cases.

In conclusion, we did not find a correlation between the total IgG4-RD RI score and the physician and patient GA in our study. Combining physician and/or patient GA into IgG4-RD RI might reflect the disease activity more accurately in children. Studies with a larger number of patients will provide more information about the applicability of these scales in children.



	At the time of diagnosis (n=8)	6th months (n=6)	1st year (n=5)	2nd year (n=5)	3rd year (n=5)	4th year (n=4)
Total IgG4-RD RI score , median	3	1	1	1	2	0,5
Total number of urgent organs, median	0	0	0	0	0	0
Total number of damaged organs, median	0	0	0	0	0	0
Total number of symptomatic organs, median	1	0	0	0	1	0
Physician GA , median	4	0	0	0	5	0
Patient GA, median	5	0,5	0	0	7	0

Fig. 1. A graph showing the median values of patients' IgG4-RD RI scores.
IgG4-RD RI: immunoglobulin G4-related disease responder index; GA: global assessment.

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