Maintenance therapy in autoimmune pancreatitis: a weak light into the darkness

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Autoimmune pancreatitis (AIP) is a fibro-inflammatory disease of the pancreas with a postulated immune-mediated mechanism (1,2). Two different histologic subtypes have been described, type 1 and type 2 AIP (3). Type 1 AIP is a more aggressive disease in terms of recurrences and extra-pancreatic organ involvement. International consensus diagnostic criteria (ICDC) have been established to classify the disease without definitive histology (4). ICDC introduced not otherwise specified (NOS) AIP as a third subtype, if type 1 or type 2 AIP cannot be diagnosed.

The main clinical aspect of AIP is the dramatic response to steroids that is a cardinal diagnostic criterion. The very high response rate to steroids observed in AIP patients, close to 100% (5), is probably related to the use of steroids as diagnostic criterion. However, the standard dosage of steroids has not been established yet because prospective randomized controlled trials are still lacking.

Different therapeutic strategies have been proposed to induce remission, from "low dose" steroids (0.2 mg/kg/day) (6) to "medium dose" 0.6 mg/kg/day (7), up to "high dose" (1 mg/kg/day) (8). Routinely, steroids administration is prolonged over a period of 2–4 weeks to achieve clinical and radiological remission and then tapered over a period of 12–16 weeks in Europe (8) and USA (9), prolonged up to 6–24 months at the dosage of 5–10 mg in Asian countries (7). The Asian strategy is based on the results of retrospective studies showing that relapse rate was significantly lower in patients treated with a maintenance dose compared to patients who discontinued steroids (7,10). A recent international consensus on the treatment of AIP (11) proposed prednisone at dosage of 0.6–1.0 mg/kg/day (level A) as initial therapy, not lower than 20 mg/day in any case (level B). The maintenance therapy with low-dose steroids or steroid-sparing agents may be useful in some patients with type 1 AIP (level B). The use of azathioprine (AZA) to prevent AIP relapse has been investigated in two recent retrospective studies, and seems to maintain remission in 70–75% of patients at 3 years (12,13). Rituximab (RTX), an anti-CD20 drug, was proposed both for induction and maintenance therapy only in type 1 AIP, with IgG4+ plasma cells in pancreatic specimens or high levels of serum IgG4 (14), and IgG4-related diseases (15).

Masamune *et al.* (16) published the first prospective randomized multicentre trial on the role of maintenance therapy with low-dosage steroids to reduce the risk of relapse in AIP. All enrolled patients (47 type 1 and 2 NOS) were randomized to maintenance arm and cessation arm, before starting steroid treatment. They were all treated with prednisolone (PSL) 0.6 mg/kg to induce remission. Then, the dose was reduced to a maintenance dose of 5–7.5 mg/kg over a period of 12 weeks, and continued for 26 weeks in both groups. There was no difference in terms of relapse rate between the two arms until week 26. PSL was continued in 30 patients at 5–7.5 mg/kg for 3 years (maintenance group), whereas discontinued in 19 patients (cessation group). Relapse rate over 3 years was significantly lower in the maintenance group (7 out of 30 patients—23.3%) than in the cessation group (11 out of 19

patients—57.9%) (P=0.011), with a hazard ratio of 0.29. No difference was reported in the development of serious adverse events (one for each group).

Some not irrelevant weaknesses have been stressed by the authors. Small sample size, the imbalance number between the two study arms (30 *vs.* 19), the use of "old" 2006 Japanese diagnostic criteria for the diagnosis, and the absence of blindness both for patients and physicians were important study limitations. However, this study presents further limitations. Pancreatic relapse was defined by imaging but type and timing of imaging modality performed were unclear. Sample size was calculated in 66 patients for each arm, and enrolled patients was therefore only 45% in maintenance group and 29% in cessation group, despite the study was extended for 1 more year due to insufficient numbers of patients recruited. Finally, the inclusion/exclusion criteria determined the enrolment of only 49 out of 131 AIP patients (37.4%) screened. Applying such criteria in clinical practice, maintenance therapy with low-dose steroids can be used in a limited number of patients. Indeed, only naïve patients were enrolled, and therefore, strictly, the results of the study cannot be applicable to previously treated AIP patients.

Despite all these weaknesses, this study represents the first randomized controlled study on the maintenance therapy for AIP and the clinical implications are therefore considerable.

Clinical management of AIP patients is still challenging, and a correct diagnosis is the pre-requisite for treatment. Pancreatic malignancy need to be excluded before treatment, particularly in AIP focal type. Steroids are generally used to induce remission representing a diagnostic criterion.

The first clinical decision-making point is to define which patients need a maintenance therapy after remission. The recent international consensus for the treatment of AIP underlines that risk factors for relapsing AIP remain poorly understood. They can be identified with (I) remarkably high serum IgG4 levels before treatment; (II) high serum IgG4 levels after steroid treatment; (III) diffuse enlargement of the pancreas; (IV) proximal type of IgG4-sclerosing cholangitis and (V) more than other two organs involved by the inflammatory process (level B—ordinarily recommendable, according GRADE system) (11). Despite this data need to be confirmed by larger prospective studies, we agree that these patients need maintenance therapy, having a risk of relapse higher than 50%.

A second key point is how to treat patients who required maintenance therapy. Although there is no "gold standard" to treat relapsing AIP, steroid, steroid-sparing agents such as immunomodulators, and RTX may be used (11). The study by Masamune *et al.* (16) suggests long-term (3 years) low-dosage steroids keep in remission 76.7% of AIP patients. This is the only controlled trial published in the literature and represents a weak light into the darkness.

AZA at dosage of 2 mg/kg/day seems to have similar percentage of sustained remission at 3 years (75%) in two small retrospective studies (12,13).

RTX administered in 2 doses (1.000 mg) at time 0 and 15 days (rheumatologic schedule) seems to be effective in IgG4-related diseases both to induce and to maintain remission in an open-label trial on 30 patients (60% with pancreatic involvement) (15). Indeed, a sustained response, defined as response maintained for more than 6 months, was observed in 73% of these patients (15). Repeated doses of RTX following a hematologic schedule (1.000 mg every week for 1 month, followed for 1.000 mg every 2–3 months for 24 months) is effective in inducing and maintaining remission (median time follow-up 10.6 months) in 10 out of 12 (83%) AIP type 1 patients studied at Mayo Clinic in USA (14).

Since the data available are poor, some considerations need to be done. Long-term low-dosage steroids, AZA or RTX are the possible choices to maintain remission high risk for disease relapse patients. Long-term low-dosage steroids approach (prednisone 5 mg/day) is probably the most largely applicable, safe, cheap and the only evidence-based treatment, even with the limitations previously stressed. The cons are the presence of diabetes and hypertension, and the negative effect on bone's metabolism. AZA has many side effects and 10% to 20% of patients are intolerant. Acute pancreatitis is a possible side effect, even though it is not reported in AIP patients, and AZA cannot be used in presence of previous malignancy. Furthermore, the onset of malignancy is reported in 10–20% of patients in the first 5 years after the clinical onset of AIP (17,18). Even if it is still unknown if this frequency is increased compared to general population (17) or not (18), a not insignificant percentage of patients will develop a cancer after the diagnosis of AIP, probably age-related. Therefore, we can suggest to pay attention to the use of AZA in older patients. RTX seems to be the most effective drug in maintaining remission but with significant limitations, especially old age and history of cancer. Furthermore, RTX is not approved by regulatory agencies for AIP, and therefore can be used only as off-label drug.

Probably the best use of long-term low-dosage steroids is in older patients. In younger patients, probably an approach with AZA may be considered. RTX may be considered in patients with a high predicted aggressive disease (other organ's involvement, particularly intra-hepatic IgG4-related cholangitis, high serum levels of IgG4).

Despite all these considerations, the lack of controlled trials doesn't allow to make any definitive conclusion.

A third key point is how long these patients need to be treated. This question is unanswered, and the duration of treatment should be decided in center with large experience in the treatment of this complex disease.

In conclusion, maintenance therapy in AIP should be tailored on single patient, considering age, personal history, comorbidities, risk of cancer, risk of disease relapse, and patient's preference for care.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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