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Immunomodulators and rituximab in the management of autoimmune pancreatitis

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Version 1.0, November 6, 2013 [DOI: 10.3998/panc.2013.20]

Introduction

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis that is characterized by a dramatic response to steroid therapy. The remission rate for induction treatment with steroids is essentially 100%, and steroids remain highly effective when used for treating disease relapses. Unfortunately, an important subset of patients have refractory disease that is difficult to treat on the basis of inability to tolerate steroids or the development of frequent relapses requiring prolonged treatment with high-dose steroids. Steroid-sparing immunomodulators, such as azathioprine and mycophenolate mofetil, were primarily introduced in an effort to manage these patients. More recently, rituximab, a monoclonal anti-CD20 antibody, has also been used in these patients, including those who were resistant or intolerant to immunomodulators. Available data suggests there may be a role for these steroid-sparing treatments, but further controlled studies are awaited to more accurately define the benefit of these agents for maintenance of disease remission.

Treatment of disease relapse

Approximately half the patients with type 1 AIP develop disease relapse within the first three years following AIP diagnosis. Although this risk may be decreased by providing long-term low-dose steroids, relapses still occur in almost one-quarter of subjects (5). The organs most frequently involved by disease relapses are the pancreas and biliary tract, and can be a significant source of morbidity. Relapses can be treated with one of four strategies, i.) tapered high-dose steroids without maintenance treatment, ii.) tapered high-dose steroids with maintenance low-dose steroids iii) tapered high-dose steroids with a maintenance steroid-sparing immunomodulator, or iv.) rituximab monotherapy. Fortunately, when steroids are used to treat disease relapse, remission is successfully reinduced in >95% of patients (3). However, some patients are either unable to successfully wean from steroids without precipitating disease recurrence or have frequent relapses, which require high dose steroid exposure for a long period of time. A small portion of patients are unable to tolerate induction treatment with high-dose steroids due short-term severe adverse effects (e.g. severe hyperglycemia or emotional/mental instability). These subsets of difficult to treat patients are most likely to benefit from steroid-sparing immunomodulators or rituximab.

Steroid-sparing immunomodulators

Immunomodulators were initially considered as a steroid-sparing alternative to long-term steroid use for maintaining disease remission. Since patients tend to present with AIP later in life, it is felt these subjects may also be more susceptible to the complications from chronic steroid use.

Table 1. Data regarding the use of immunomodulators in treatment of AIP published prior to 2010.

Author; Country	n	Achieved steroid-free remission (n)	Disease relapses (n)	Median follow-up, (range)	Drugs used (n)	Comments
Ghazale et al.(2); United States	7	7/7	2*	6 mos, (2-19)	AZA(4), MMF(2), CTX(1)	*Both relapses occurred while patients were taking low dose AZA
Sandanayake et al.(11); United Kingdom	10	7/8*	0	4 mos, (1-36)	AZA	*2 patients started on AZA and steroids did not have follow-up
Raina et al.(9); United States	10	10/10	1*	NR	AZA(9), MTX(1)	*2 additional patients later had relapses <2 months after AZA discontinuation
Frulloni et al.(1); Italy	6	6/6	0	17 mos (6-36)	AZA(4), MTX(2)	

AZA, azathioprine; CTX, cyclophosphamide; MMF, mycophenolate mofetil, NR, not reported

Four case series were published in the late 2000's describing the effectiveness of immunomodulators in AIP (1, 2, 9, 11). In each study the clinical response to initial treatment with immunomodulators was consistently high **(Table 1).** Almost all patients were able to achieve clinical remission, and only a small number of subjects developed a disease relapse, which typically followed discontinuation of the immunomodulator. However, in these studies a variety of agents was used (azathioprine, mycophenolate mofetil, and methotrexate), the sample sizes were small, and median follow-up times were relatively brief.

More recently we evaluated our experience treating 41 AIP subjects with immunomodulators at Mayo Clinic (4). Azathioprine (dosed at 2 mg/kg/day) was the most commonly used immunomodulator, followed by 6-mercaptopurine (1 mg/kg/day) and mycophenolate mofetil (750-1,000 mg twice daily). Relapse free survival was similar between those patients who were treated with steroids alone compared to steroids and an immunomodulator at the time of their first disease relapse **(Figure 1).** Although there was a trend towards longer remission in those who received immunomodulators, this did not achieve statistical significance.

Importantly, a significant number of patients either developed immunomodulator resistance (i.e., development of a relapse while on the immunomodulator or inability to wean prednisone) or did not tolerate the side effects of this treatment. During the study period 17 patients were either resistant (n=15) or intolerant (n=2) to immunomodulator treatment. Also, 9 (22%) patients required drug discontinuation due to side effects including nausea/vomiting, drug-induced liver injury, myelosuppression, and bacteremia. Many of these patients were able to tolerate substitution with either another thiopurine or mycophenolate mofetil. Steroid-sparing immunomodulators may have a modest benefit in some patients, but there remains a group of refractory patients who cannot be satisfactorily maintained in remission with immunomodulators.

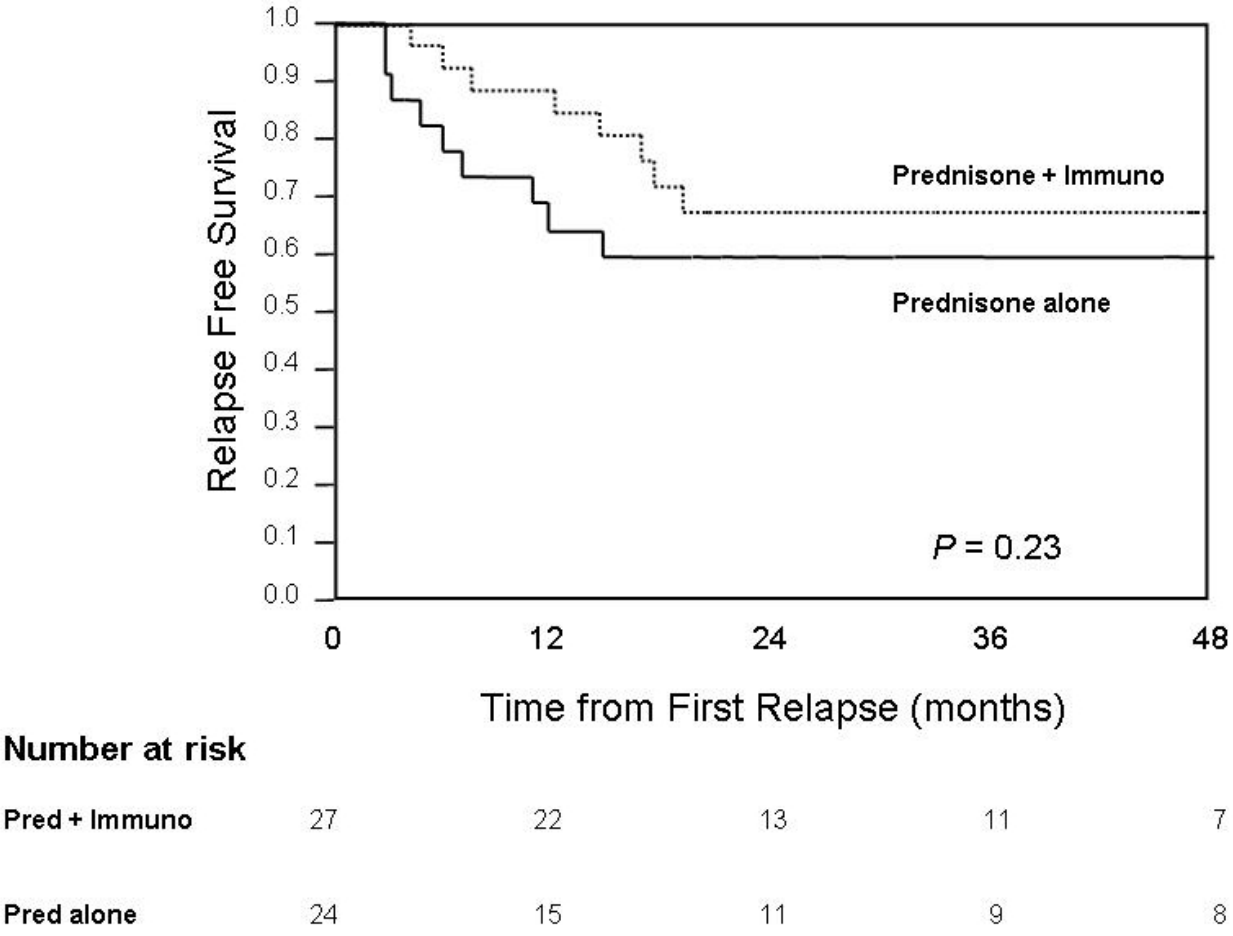

Figure 1. Relapse free survival following treatment of initial disease relapse with either tapered prednisone alone, or tapered prednisone plus an immunomodulator for maintenance treatment. Used with permission from Hart et al.(4)

Rituximab

An important breakthrough occurred when rituximab, a monoclonal anti-CD20 antibody, was demonstrated to successfully treat a patient with refractory AIP (13). This complicated patient had recurrent intrahepatic biliary disease, was unable to tolerate steroids (due to a serious infection), and subsequently developed a relapse during treatment with a thiopurine. The observation was made that there were abundant CD-20 staining lymphocytes on a pancreas biopsy, analogous to the findings seen in orbital pseudolymphoma (a disease known to respond to rituximab) (15). After a series of 4 infusions the patient had an impressive clinical and radiographic response.

Since the initial report we have continued to use rituximab in these difficult-to-treat patients by providing a series of infusions over two years. The protocol consists of administering 375 mg/m^2 (BSA) intravenously weekly for four weeks, followed by eight additional maintenance infusions every three months (a protocol that is similar to treatment of B-cell lymphoma). We reported that 10 out of 12 patients who had completed at least the four induction infusions achieved a convincing symptomatic, biochemical, and radiographic remission (4). One patient had a partial response and was later found to have an alternative, but concurrent diagnosis to explain his lack of response. None of the patients developed a disease relapse during rituximab treatment. One subject did develop a pancreatic relapse more

than two years after discontinuing rituximab, which remained responsive to readministration of rituximab.

Rituximab has also been shown to be effective in subjects with IgG4-related disease without pancreatic-predominant disease. Khosroshahi *et al*. reported their experience treating 10 patients, the majority of which had systemic IgG4-related disease manifestations such as salivary gland involvement, orbital disease, or lymphadenopathy (n=2 had biliary and/or pancreatic involvement) (6). The rituximab protocol used in this study consisted of two infusions of 1,000 mg administered intravenously on days 0 and 14, with no maintenance infusions (a protocol that is similar to treatment of rheumatologic conditions). Nine of these 10 patients had clinical improvement within one month of treatment, however 4 patients required retreatment within 6 months due to disease relapse.

Although it has been shown to be effective as a first-line agent, due to cost and limited experience we have reserved its use for difficult to treat patients. Also, the optimal dosing regimen and durability of this response is unknown. Currently a phase I/II open-label study using the two dose protocol is underway and will hopefully shed light on these areas of uncertainty (NCT01584388).

Treatment-related complications

Since steroids are excellent at controlling disease and inexpensive, any alternative treatment must not only be effective, but also offer a more favorable side effect profile than steroids. Due to the rarity of AIP there are no large studies describing long-term side effects of immunomodulators. However, these agents have been well studied in rheumatologic and inflammatory GI conditions (such as inflammatory bowel disease and autoimmune hepatitis). Common side effects of azathioprine (and 6-mercaptopurine) include nausea, myelosuppression, hepatotoxicity, increased risk of infections, and pancreatitis (12). Mycophenolate mofetil can also lead to a variety of side effects including headache, diarrhea, edema, leukopenia, and increased risk of infections (14). When taken for many years these medications also increase the risk of lymphoma and nonmelanoma skin cancers (8, 14). As previously discussed, in the Mayo Clinic immunomodulator study almost a quarter of patients started on an immunomodulator required drug discontinuation due to intolerable side effects, so vigilance for the development of complications is warranted.

Likewise data regarding the use of rituximab in AIP are too limited to provide a meaningful assessment of any disease-specific side effects; however these risks have been extensively studied in the treatment of lymphoma and rheumatoid arthritis. In these studies rituximab is generally safe and well-tolerated. The most common complication is a cytokine-mediated infusion reaction consisting of flu-like symptoms. This develops in 10% of subjects during the initial infusion, and resolves with cessation of the infusion and supportive measures (7). True allergic reactions with hypotension and bronchospasm are exceedingly uncommon. Reactivation of chronic hepatitis B and C can occur, so hepatitis serologies should be checked prior to treatment (7). Other rare, but possible, late adverse events include interstitial pneumonitis, delayed-onset neutropenia, and progressive multifocal leukoencephalopathy (10).

Summary

Although AIP disease activity is generally well-controlled with intermittent high-dose or chronic low-dose steroids, there is a subset of difficult to treat patients who require an alternative treatment strategy. Rituximab is highly effective for both induction and maintenance of remission, however due to high costs it is generally reserved for refractory patients. For those who develop frequent relapses or are unable to be weaned from steroids, we generally administer azathioprine or another steroid-sparing

immunomodulator. In patients who are either unable to tolerate the immunomodulator or relapse during immunomodulator treatment there are no other options aside from rituximab treatment. Our current algorithm for managing relapsing AIP is shown in **Figure 2**. This treatment approach is based on observational data and clinical experience. More rigorous, controlled trials investigating different means of maintaining disease remission in AIP are needed to refine this treatment strategy.

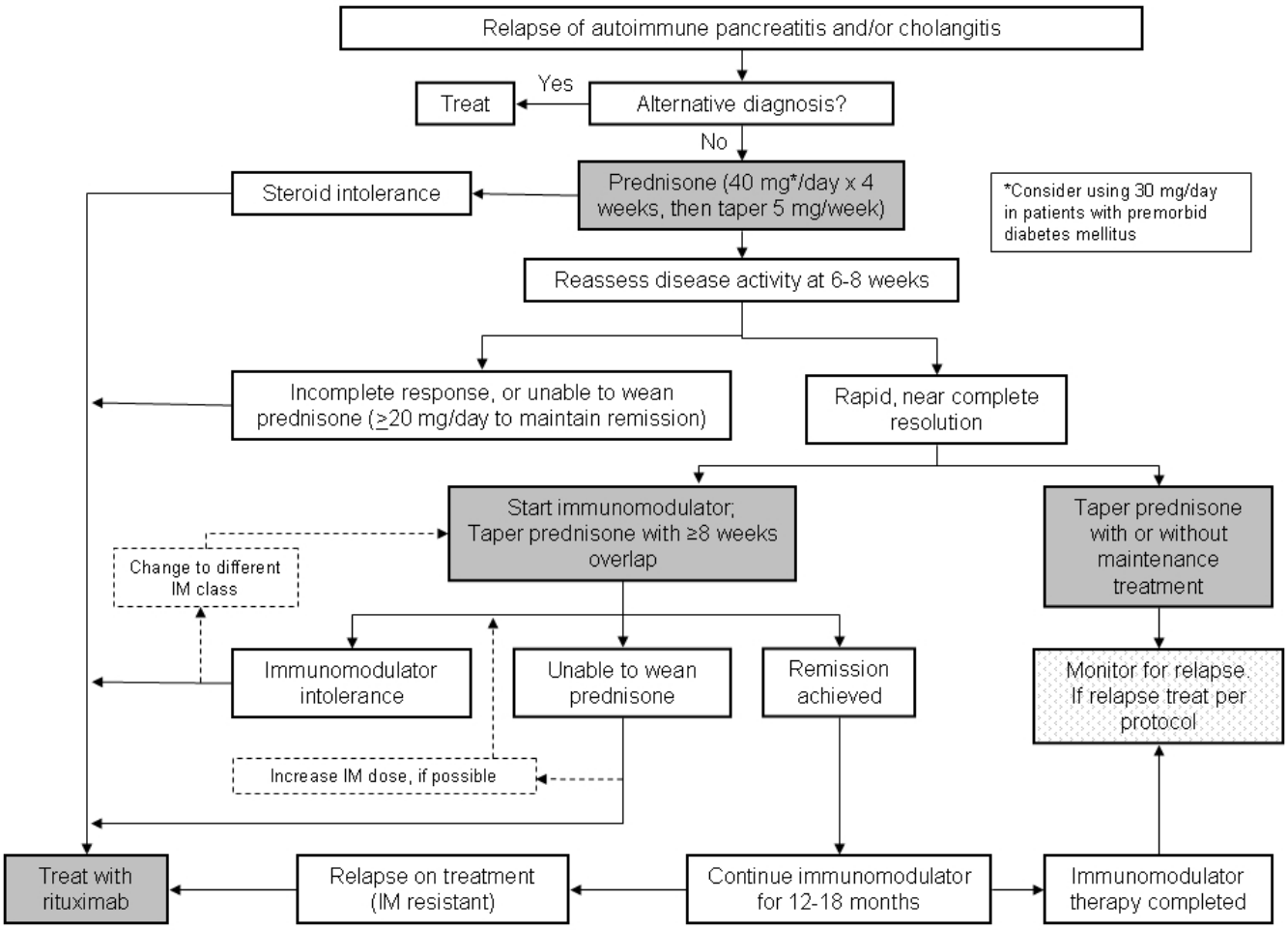

Figure 2. Algorithm for management of disease relapses for patients with AIP. Used with permission from Hart et al.(4)

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