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"Hit me with your best shot…Fire away!"

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Taking the line "Hit me with your best shot… Fire away!" from a Pat Benatar song, it seems that early, aggressive therapy for various autoimmune illnesses provides an opportunity for disease modification or, possibly, disease reversal (potential cure?). There is evidence that, even without identification of the initiating antigen or antigens, endogenous stem cells can replace cells damaged by an immune response and restore their function. In a mouse model of type 1 diabetes, adjuvant-dependent dampening of an autoimmune attack can be coupled with recovery of host islet cells to restore beta-cell mass (Melton D [2006] *N Engl J Med* 355: 89–90).

Early intervention seems to modify the subsequent disease course of both multiple sclerosis and rheumatoid arthritis. Optic neuritis is the presenting feature in 15–20% of patients with multiple sclerosis, occurring sometime during the disease course in 50% of patients. Patients randomly allocated within 8 days of onset of acute, inflammatory optic neuritis to receive high doses of intravenous methylprednisolone, with or without interferon β, had a significantly reduced 2-year progression rate to multiple sclerosis (Balcer LJ [2006] *N Engl J Med* 354: 1273–1280). Similarly, early treatment of rheumatoid arthritis, before joint erosions have developed, with combination methotrexate and biologic agents (primarily anti-TNF agents), can reduce or prevent the development of joint deformity—at least for several years (Emery P [2006] *BMJ* 332: 152–155).

Similar data are emerging for Crohn's disease. Although the introduction of biologic therapies has been investigated in patients with moderate to severe and usually refractory disease, there is evidence that when immune-directed therapy is introduced earlier in the disease course, the long-term behavior of Crohn's disease can be 'modified'. A hint of this potential is suggested by the observation that the proportion of patients reaching a given outcome can differ by orders of magnitude when studies of thiopurine antimetabolites are compared. In an adult population with refractory Crohn's disease, combination therapy with corticosteroid induction and azathioprine maintenance therapies resulted in 42% of patients on azathioprine versus 7% of patients on placebo maintaining remission at 15 months (Candy S *et al*. [1995] *Gut* 37: 674–678). By contrast, when a pediatric population with early onset, corticosteroid-naive Crohn's disease was randomly allocated to corticosteroids, either with or without mercaptopurine, only 9% of patients who achieved remission relapsed while on mercaptopurine, compared with 47% of controls (Markowitz J *et al*. [2000] *Gastroenterology* 119: 895–902). So, although absolute response rates were similar, the response curves were 'shifted up' in the pediatric population.

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Early intervention with biologic therapy for Crohn's disease has been presented as part of the 'top-down' versus 'step-up' induction trial reported at UEGW 2005 and DDW 2006. Patients with early onset (steroid-naive) Crohn's disease who were randomly allocated to induction therapy with infliximab, followed by azathioprine maintenance, had significantly better mucosal healing after 2 years than patients who commenced therapy with corticosteroid therapy and advanced to azathioprine or infliximab only after failing steroid tapering (Hommes D *et al*. [2006] *Gastroenterology* 130: A-108 [abstract #749]).

The future is bright for patients with chronic inflammatory diseases. Of course, the diverse risks of disease progression and potential risks of early intervention with biologic and/or immune-suppressive therapy mean that appropriate selection of patients for 'best shot' early intervention will be critical for each disease state considered.

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Competing interests
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