

SELECTED SUMMARIES

Immunosuppressant Combined with Infliximab in Crohn's Disease: For 6 Months, for 2 Years, or Forever?

Oussalah A, Chevaux J-B, Fay R, Sandborn WJ, Bigard MA, Peyrin-Biroulet L. Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy. *Am J Gastroenterol*. 2010;105:1142–1149.

The recently published article by Oussalah et al reports a retrospective analysis of a single-center cohort of 48 patients with luminal Crohn's disease (CD) treated by combined therapy with infliximab and azathioprine for at least 6 months and who then stopped azathioprine after a mean of 30.2 months of combined therapy. The primary aim of the study was to analyze predictive factors of infliximab failure after azathioprine withdrawal. Infliximab failure was defined either as a disease flare requiring shortening of the dosing interval or increasing the infliximab dose to 10 mg/kg, or switching to adalimumab, as acute or delayed hypersensitivity reactions leading to infliximab discontinuation, or as CD-related surgery. The survival probabilities without infliximab failure were 85% ($\pm 5\%$) at 12 months and 41% ($\pm 18\%$) at both 24 and 32 months. Independent predictive factors of infliximab failures were combined therapy exposure < 811 days, C-reactive protein (CRP) > 5 mg/L, and platelet counts $> 298 \times 10^9/L$.

COMMENTS

Although the study by Oussalah et al is retrospective and relatively small-sized, it tackles a very important and relevant question. After publication of the results of the SONIC trial, combination therapy with antitumor necrosis factor (TNF) and immunosuppressant has been recognized as the most efficacious option to treat early severe immunosuppressant-naïve CD patients.¹ Although evidence to do the same in patients having failed immunosuppressant is lacking, it has also become a broadly used treatment option in this setting. However, most patients and physicians are concerned about safety issues, mainly the risk of opportunistic infections and lymphoma, which could appear with such long-term treatment. Therefore, solutions for treatment deescalation are currently explored in prospective and retrospective studies. In the previously pub-

lished controlled trial comparing immunosuppressant withdrawal after 6 months of combined therapy with infliximab to continued combined therapy, no significant difference in infliximab failure was found between the two groups over a follow-up of 2 years.² However, CRP concentrations were significantly higher and infliximab trough levels significantly lower in patients having withdrawn azathioprine. As these features have been associated with an increased risk of treatment failure, a doubt remains about the long-term sustained benefit with infliximab monotherapy. In the present study, Oussalah et al found a relapse rate after azathioprine withdrawal very similar to the one found in the IMID study with or without azathioprine withdrawal.^{2,3} Interestingly, they could identify predictive factors of relapse: essentially shorter duration of combined therapy and persistent signs of inflammation, i.e., elevated CRP and platelet counts. Biological signs of inflammation have already been associated with the risk of relapse after azathioprine withdrawal in a different clinical setting.⁴ The limitation of the present study is that there is no proof that these factors are really predictive of relapse after azathioprine cessation or more broadly predictive of relapse under infliximab treatment. Indeed, as there is currently no proof of an excess of relapse when withdrawing azathioprine beyond 6 months of combined therapy, the relapse may have occurred in the same patients even if combined therapy had been continued. Particularly, persistent signs of inflammation are a nonspecific marker for higher risk of relapse in CD and, interestingly, it is not the duration of azathioprine therapy that was associated with a risk of relapse but rather the duration of infliximab therapy (the duration of combined therapy in the present study was most probably equivalent to a duration of infliximab therapy, as only 2/48 patients started azathioprine after infliximab). Yet, globally patients having been in stable remission over long-term infliximab are probably at low risk of relapse because they are responding particularly well to this drug and probably less prone to develop immunization against the drug. In other words, this study does not permit conclusions about the optimal duration of combined therapy and in particular does not demonstrate that one should

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wait for at least 27 months before stopping azathioprine. It also does not show that stopping azathioprine in patients with elevated CRP or platelet count increases their risk of relapse.

Therefore, although this study confirms that patients in stable remission after prolonged combined treatment with infliximab and azathioprine and having a low level of systemic inflammation have a low risk of relapse, it leaves us with an unresolved question as to whether we should use combined therapy for more than 6 months, and even whether we should use it in place of anti-TNF monotherapy in case of immunosuppressant failure. Ultimately, a firm response to this important question would require a properly designed prospective controlled trial.

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