Crohn’s disease is a lifelong, disabling disorder with 2/3rd of patients requiring surgery in their lifetime.\(^1,2\)

In 1998, introduction of anti-TNF-α agents to treat Crohn’s disease was a tremendous medical advance.\(^3\)

Anti-TNF-α treatment promotes complete mucosal healing in ~50% of pts & remission rates of 40-50% are expected in patients with mod-severe disease.\(^4,5,6\)

Concerns for increased rates of opportunistic infections, lymphoma and splenic T-cell lymphoma have tempered enthusiastic use of anti-TNF-α agents, especially in combination with azathioprine (AZA) and 6-mercaptopurine (6MP).\(^7,8,9\)

The study by Colombel and the Sonic Study group reviewed in this edition of www.VHJOE.org scientifically confirms, infliximab (IFX)-AZA combination therapy is more effective and as safe as mono therapy with either IFX or AZA.\(^10\)

**Comments:**

Colombel, and the other members of the SONIC Study Group are praised for conducting a much needed study on the efficacy of IFX + AZA vs. mono therapy with IFX or AZA in patients with mod-severe Crohn’s disease.\(^10\)

The investigators’ research shows that IFX + AZA is clearly more effective than mono therapy with IFX or AZA and in the short term (12 months), and just as safe. However, Colombel, et al, fail to answer the following questions: Are the short term “6-12 mo” improved efficacy and reduced serious infections seen with IFX + AZA durable? Will greater than 12 mo of IFX + AZA therapy prove to be the “Achilles’ heel,” with increased development of serious infections and malignancy in long term?

The greater remission rates for IFX + AZA vs. IFX + PBO seen in this study, may be related to reduced immunogenicity toward the chimeric anti-TNF-α (IFX), as ATI’s are reduced and trough levels of IFX are higher in the combined IFX-AZA group.

<table>
<thead>
<tr>
<th></th>
<th>IFX + AZA</th>
<th>IFX + PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATI</td>
<td>0.9%</td>
<td>14.6%</td>
</tr>
<tr>
<td>Trough IFX</td>
<td>3.5 μg/ml</td>
<td>1.6 μg/ml</td>
</tr>
</tbody>
</table>

Interestingly, many studies of biologic therapy among Crohn’s disease patients have shown that the initiation of therapy earlier in the onset of the disease predicts much higher remission rates.\(^11,12\)

The “Sonic Trial” study evaluated patients with short duration of Crohn’s disease and naive to biologic and immunomodulator therapy.\(^10\) The “high” ~60% remission rate for IFX + AZA seen in the Sonic Trial may be attributable to selection bias, since subjects enrolled in the Sonic trial we all naive of prior AZA, MTX and biologic therapy and their duration of disease was short, average 2.3 yrs.

Immunogenicity of the 3 FDA approved anti-TNF-α agents (IFX, ADA, and CTZ) is different.\(^13\)

It is very important to emphasize that the remission rates for ADA + AZA or CTZ + AZA cannot be assumed to be the same as seen with IFX + AZA in the Sonic Trial! Likewise, safety for ADA + AZA or CTZ + AZA cannot be assumed to be the same as seen with IFX + AZA in the Sonic Trial!

Unfortunately, the Sonic Trial does not address the question, “is there an exit strategy?” It is very important to determine if combo IFX + AZA treatment can be “stepped-down” to just IFX or AZA after 1-2 years of “deep remission” with endoscopic confirmed mucosal healing.
Conclusions:

Crohn’s disease is an incredibly devastating and debilitating disorder. The Sonic trial results are specific for IFX + AZA and should not be empirically applied to ADA + AZA or CTZ + AZA. More work needs to be done to develop a stratified treatment strategy, that will balance risks of combination IFX + AZA therapy with benefits of disease suppression.

Future Treatment strategies for Crohn’s disease should be guided by:

- Staging Criteria = Montreal Criteria
- Genetic Markers = NOD2 (SNP8, SNP12, SNP13)
- Antibodies to gut microbiota (ASCA, OmpC, CBir1, Anti-I2, PANCA)
- Serial assessment for mucosal healing

References:


