Anson W. Lowe and Richard H. Moseley, Section Editors

Infliximab Dosing for Patients With Inflammatory Bowel Disease, Based on Trough Levels

The use of biological agents has been a major advance in the treatment of patients with inflammatory bowel disease. For example, weight-based dosing (5 mg/kg) of the chimeric immunoglobulin (Ig)G1 monoclonal anti-tumor necrosis factor antibody, infliximab, involving an induction phase followed by maintenance treatment has been shown to be effective in inducing and maintaining clinical remission in patients with Crohn's disease (CD) and ulcerative colitis (UC). However, over time, therapeutic benefit is lost in many patients, requiring a dose escalation or a switch to another biological agent. This loss in therapeutic benefit has been shown to be associated with low serum infliximab trough concentrations (TCs), with or without the development of antibodies to infliximab, and individualized dose adjustment has been shown to be more cost effective, but the effect of adjusting dosing based on monitoring infliximab levels has not been previously prospectively studied.

In this issue of *Gastroenterology* (accompanied by an editorial by Shomron Ben-Horin), Vande Casteele et al report the findings of the Trough concentration Adapted infliXImab Treatment (TAXIT) trial, which compares the efficacy, cost effectiveness, and safety of concentration-based dosing with clinically based dosing of infliximab in patients with CD and UC on maintenance treatment. All 263 patients enrolled (178 with CD and 85 with UC) were first optimized to attain a target TC of 3-7 μg/mL, after which subsequent infliximab dosing was based on their clinical features (symptoms and C-reactive protein levels) or dosing based on TCs. Out of the 263 patients, 76 patients had TCs of <3 μg/mL. Dose escalation to a TC of 3-7 μg/mL was achieved in 69 patients (91%) during this optimization phase and resulted in a higher proportion of patients with CD in remission and a decrease in the median concentration of C-reactive protein; this effect was not observed in patients with UC. In contrast, in 72 patients with TCs $>$ 7 μg/mL, 67 (93%) patients achieved TCs of 3-7 μg/mL after dose reduction, resulting in a 28% reduction in drug cost (Figure 1).

After the optimization phase, during the 1-year randomized maintenance phase, there was no difference in achieving remission, the primary end point of the study, in patients assigned to dosing based on clinical features (66%) compared with patients whose dosing was based on TCs (69%). However, disease relapsed more often in patients who received clinically based dosing (17% vs 7%). These findings demonstrate that targeting infliximab TCs to 3-7 μg/mL in patients with CD results in a more efficient use of the drug. Although, after dose optimization, continued concentration-based dosing for 1 year was no better than clinically based dosing, it was associated with fewer relapses requiring rescue therapy.

See page 1320; editorial on page 1268.

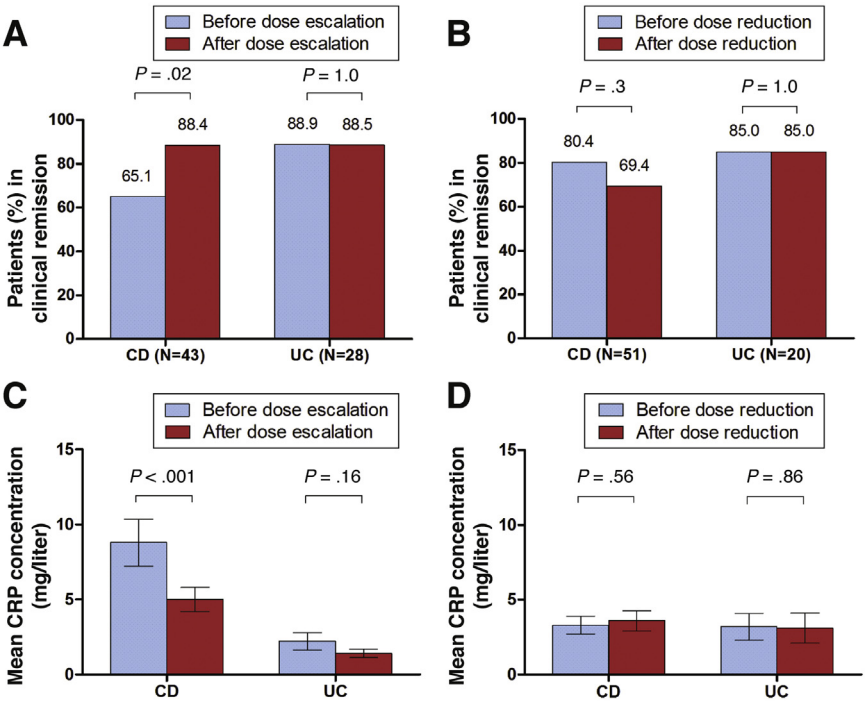

Figure 1. Illustrates the effect of concentration-based dose escalation (*A*, *C*) and dose reduction (*B*, *D*) during the optimization phase on the proportion of patients in remission (*A*, *B*) and on the CRP concentration (mg/L) (*C*, *D*) for patients with CD and UC. Patients who discontinued the optimization phase due to personal reasons (ie, noncompliant with treatment algorithm or consent withdrawal) were excluded from the analysis (1 CD and 4 UC patients from the dose-escalation group and 1 UC patient from the dose-reduction group). Remission was defined as an HBI $\leq$4 or PMS $\leq$2 with no individual subscore of $>$1.

Drug-Induced Liver Injury: Outcomes and Incidence

Idiosyncratic drug-induced liver injury (DILI) is among the leading causes of acute liver failure and remains a major impediment for new drug development and marketing. In this issue of *Gastroenterology* (accompanied by an editorial by Rolf Teschke and Raul J. Andrade), 2 studies focus on this important topic.

Although DILI is recognized as a common cause of acute liver failure, there have been no population-based studies to evaluate specifically the incidence, characteristics, and outcomes of drug-induced acute liver failure. Goldberg et al conducted a retrospective cohort study using data, over a 7-year period, from the Kaiser Permanente Northern California health care system, an integrated health organization providing comprehensive inpatient and outpatient services to >5 million covered individuals that approximates a population-based cohort. Of 62 inpatients categorized as having definite or possible acute liver failure, 32 (52%) had a drug-induced cause. Acetaminophen was implicated in 18 events, herbal or dietary supplements in 6, and antimicrobials in 2. Four patients died and 6 underwent liver transplantation. The incidence rates of any definite drug-induced acute liver failure and acetaminophen-induced acute liver failure were 1.61 events per 1,000,000 person-years and 1.02 events per 1,000,000 person-years, respectively.

The Drug Induced Liver Injury Network, a consortium of several academic institutions in the United States, has previously described their findings on the initial 300 patients enrolled in their prospective study of patients with suspected non–acetaminophen-related DILI. Antimicrobials and herbal or dietary supplements were found to be the most commonly implicated agents; acute DILI was associated with an 8% risk of mortality and a 13% risk of injury 6 months after onset. Acute infection with hepatitis C and E virus can mimic DILI. Chalasani et al now report their findings with the first 1257 patients enrolled in this study, 899 of whom were considered to have definite, highly likely, or probable DILI. Antimicrobials were the 9 most commonly implicated agents, although herbal and dietary supplements, as a class, were the second most common implicated agent (Table 1). Ten percent of patients died or underwent liver transplantation, an outcome that was more common in patients with hepatocellular injury and 18% developed chronic injury, an outcome that was more common in patients with cholestatic injury. Patients with mixed injury had the most favorable prognosis and outcomes. Older individuals (≥65 years) were more likely to have cholestatic injury, although mortality or the rate of liver transplantation was no different in this age group. Mortality was extremely high in patients with DILI and concomitant severe skin reactions. Compared with patients without liver disease, patients with preexisting liver disease had significantly greater mortality rates (16% vs 5%), and azithromycin was implicated in more of these patients (7% vs 2%). Latency of ≤7 days was most commonly associated with antimicrobials and the 2 most common causes for latency of >365 days were nitrofurantoin and minocycline; however, there was no difference in outcomes of patients with short versus long latency.

These 2 studies add to the expanding number of publications on DILI with 1 common thread to both—the increasing role of herbal agents and dietary supplements in causing severe DILI.

See pages 1340 and 1353; editorial on page 1271.

Table 1. Top 10 Therapeutic Classes and Individual Agents to Cause Drug-Induced Livery Injury in The DILIN Prospective Study

	Therapeutic classes	n		Individual agents[a]	n
1	Antimicrobials	408	1	Amoxicillin-clavulanate	91
2	Herbal and dietary supplements	145	2	Isoniazid	48
3	Cardiovascular agents	88	3	Nitrofurantoin	42
4	Central nervous system agents	82	4	Sulfamethoxazole/trimethoprim	31
5	Anti-neoplastic agents	49	5	Minocycline	28
6	Analgesics	33	6	Cefazolin	20
7	Immunomodulatory	27	7	Azithromycin	18
8	Endocrine	20	8	Ciprofloxacin	16
9	Rheumatologic	13	9	Levofloxacin	13
10	Gastrointestinal	12	10	Diclofenac	12

[a]Herbal and dietary supplements are not included. Also, in cases of multiple implicated agents, the primary implicated agent was considered for this analysis.

Active Transforming Growth Factor-β Signaling Despite Mutations in its Receptor, TGFBR2

The transforming growth factor (TGF)-β signaling pathway has been implicated in the suppression and promotion of colon cancer. TGF-β binds to the TGFBR2 receptor, which results in the activation of a signaling cascade that activates or represses gene transcription.

Fifteen percent of colorectal cancers exhibit a high level of microsatellite instability (MSI-H), which is caused by mutations in DNA mismatched repair genes and results in errors throughout the genome. Mutations within a microsatellite sequence normally containing 10 adenines within the third exon of *TGFBR2* is present in the majority of MSI-H colon cancers. The *TGFBR2* mutations observed are