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MÅNADENS REDAKTÖR

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25 years of anti-TNF treatment for inflammatory bowel disease: lessons from the past and a look to the future

Geert R D'Haens GR, van Deventer S. Gut 2021;70:1396–1405.

A very interesting article describing the 25 year long history of TNF-inhibitors starting with the authors own first experiences with infliximab. The lessons from the past are presented as easy to grasp boxes. Regarding the future they conclude that anti-TNFs remain as the preferred treatment option. The authors claim that infliximab is the drug of choice in severe ulcerative colitis given ites rapid effect. It is also expected that novel subcutaneous IFX preparations will sonn be available.

In the predictable future, they expect predictive biomarkers to become clinically validated. The authors therefore remain convinced that at least in the coming decade TNFi will continue to be very important treatments for IBD.

GUT HEALTH
LEGACY, COMMITMENT, INNOVATION

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Rational Combination Therapy to Overcome the Plateau of Drug Efficacy in Inflammatory Bowel Disease

Stalgis C, Deepak P, Mehandru S, Colombel J-F. Gastroenterology 2021;161:394–399.

In this commentary published in Gastroenterology the authors discuss new possibilities to improve therapeutic outcome in the drug treatment of inflammatory bowel disease. They claim that todays drug therapy is suboptimal and give a number of examples. Approximately 30% of patients are primary responders to initial treatment and further on about 50% of patients loose response to drugs. In other words, the authors state that there seem to be a ceiling effect between 26 to 59 percent responders. With that background they give examples on different ways to overcome the plateau. The way forward is, on short term, combining therapies (drugs) with complementary mechanisms of action. Several suggestions are given. First of all the already known benefit of combining anti-TNFs with thiopurines. Other examples are combination of JAK-inhibitors with anti-Interleukin compounds, both anti IL-12/23 or anti IL-23. Yet another possibility would be combination of anti-TNF eller anti-IL with antileukocyte trafficking agents. The forth alternative presented is any anti-inflammatory drug combined with metabolomic or microbiome based therapeutic.

REFLECTION

My reflection is that the authors have a good point. My opinion is that we are obliged to use combination therapy of the drugs available while waiting for new drugs to be launched. To day there is a clear lack of studies on combination therapy to guide us. The suggestions given in this article give some useful guidelines on how we can combine different drugs.

Dual Biologic and Small Molecule Therapy for the Treatment of Refractory Pediatric Inflammatory Bowel Disease

Dolinger MT, Spencer EA, Lai J, Dunkin D, Dubinsky, MC. Inflamm Bowel Dis2021;27(8):1210-1214.

This is an observational study aiming to assess the efficacy and safety of concomitant use of two biologic compunds or combination of biologic and tofacitinib in a treatment refractory pediatric cohort. Steroid-free remission at six months was the primary endpoint. Time to steroid-free remission, change in CRP, SR and albumin from baseline to six months and adverse events.

The study is ongoing and the authors report the results for the first 16 patients., all failing at least two biologic agents. Nine of patients had UC/IBD-U and seven CD. Vedolizumab and Tofacitinib was given to 9 patients (53%). Ustekinumab and vedolizumab was given to 4 patients (25%) and finally ustekinumab and tofacitinib to 3 patients (19%).

Twelve of the 16 patients, 75%, reached steroid-free remission at six months, of them seven with UC/IBD-U and five with CD.

CRP, SR and albumin improved significantly between baseline and six months.

One patient on the combination of vedolizumab, tofacitinib and prednisone developed septic arthritis and a deep vein thrombosis.

The authors conclude that their data suggest that dual therapy may be an option for patients with limited therapeutic options remaining and that larger controlled prospective clinical studies both in adults and children is needed.

(Reflection on page 3) ▶

REFLECTION

My reflection is that my request presented above was granted. Even when taking the very small number of patients and relatively short time into consideration, this study give support to combine drugs. In this study 75% of the patients could avoid surgery, at least on a short term, with some safety concerns.

Combination Therapy Does Not Improve Rate of Clinical or Endoscopic Remission in Patients with Inflammatory Bowel Diseases Treated With Vedolizumab or Ustekinumab

Anne Hu A, Kotze PG, Burgevin A,Tan W, Jess A, Li P-S, Kroeker K, Halloran B, Panaccione, R, Peyrin-Biroulet L, Ma CAnanthakrishnan AN. Clinical Gastroenterology and Hepatology 2021;19:1366–1376.

Design: A retrospective study of patients with Crohns diseases or Ulcerative colitis starting treatment with vedolizumab or ustekinumab at Massachusetts General Hospital (USA), Alberta Health sciences (Canada) or Nancy University Hospital (France) with at least one year of follow up.

Primary outcome clinical remission or clinical response at week 14 based on the Harvey Bradshaw Index for CD or simple clinical colitis index or partial Mayo score for UC. Clinical outcomes, endoscopic response and durability of therapy was also examined at week 30 and week 54.

A total number of 912 patients were included 549 (263 with UC and 286 with CD) received vedolizumab and 363 (4 with UC and 359 with CD) received ustekinumab.

Combination therapy was given to 251 patients. Of them, 131 had vedolizumab (thiopurins n=78, methotrexate n=53) and 120 ustekinumab (thiopurines n=57, methotrexate n=63). The remaining 661 patients were consequently not on combination therapy.

For vedolizumab, there was no difference in clinical response or remission with combination therapy vs monotherapy at week 14 (68.2% vs 74.1%; p=0.22), week 30 (74.3% vs 75.6%; p=0.78) or week 54 (78.3% vs 72.9%, p=0.33).

For ustekinumab, there was no difference in clinical response or remission with combination therapy vs monotherapy at week 14 (54.6% vs 65.8%; p=0.08), week 30 (71.6% vs 77.4%; p=0.33) or week 54 (62.1% vs 67.0%; p=0.52).

Subgroup analysis by IBD type, biologic-naive or biologic-experienced status, and type of immunomodulato was performed and showed no incremental benefit of combination therapy, for UC as well as CD.

There were similar proportions of patients remaining on treatment or with endoscopic response at 1 year among patients receiving combination or monotherapy with vedolizumab or ustekinumab.

The authors conclude that In patients with CD or UC initiating ustekinumab or vedolizumab therapy, combination therapy with immunomodulators did not increase rates of clinical remission or response, endoscopic remission, or persistence of therapy at 1 year.

REFLECTION

My reflection is that patients treated with ustekinumab or vedolizumab seem not to benefit from combination therapy with thiopurines or methotrexate. However, there is a recent publication in Journal of Gastroenterology and Hepatology evaluating potential benefits of immunomodulator use with vedolizumab for maintenance of remission in ulcerative colitis, see below. Moreover, a randomized and double-blind controlled trial on combination therapy is needed before a definite statement on the benefits of combination therapy could be given.

Potential benefits of immunomodulator use with for maintenance of remission in ulcerative colitis

Naganuma M,Kenji Watanabe K, Motoya S, Ogata H, Matsui T, Suzuki Y, Ursos L, Sakamoto S, Shikamura M, Hori T, Fernandez J, Watanabe M, Hibi T, Kanai T. Journal of Gastroentrology and Hepatology 2021. doi:10.1111/jgh.15667.

Design: Retrospective analysis of patients enrolled in a phase 3 study conducted in Japan (NCT 02039505). The original study was published in PLosOne 2019.

Efficacy endpoints. Rates of clinical reponse, clinical remission and mucosal healing at week 60 were analyzed in subgroups by concomitant IM use at week 0.

At week 60, clinical remission was achieved by 68.2% of the patients with immunomodulators (IMM) at start compared to 42.1% of the patients without IMM. The difference between the groups 26.1 with a 95% confidence interval of (-3.5 to 55.6). For mucosal healing the results were 77.3% and 47.4% respectively, giving a delta at 29.9 with 95% confidence interval (1.4 – 58.4). As far as I can judge the results are statistically significant for mucosal healing but not for clinical remission.

164 patients were included in total, of them 80 had concomitant treatment with immunomodulators (azathioprine 64 and 6-merkaptopurine 16).

The authors conclude that the results suggest the possibility that concomitant immunomodulator use may be beneficial to maintain the clinical efficacy of vedolizumab for treatment of ulcerative colitis.

A Phase 2 Randomized Controlled Trial Demonstrating the Efficacy and Safety of SHR0302, A Selective JAK1 Inhibitor for the Treatment of Moderate to Severe Ulcerative Colitis Patients.

Chen B, Zhong J, Cao Q, Li X, Pan F, Li S, Ding Y, Goh AH, Chen X, Rubin DT, Sandborn WJ, Chen M.Gastroenterology 2021;161(2):e29-e30.

This is an abstract describing the results from the AMBER2-study, a global, randomized and placebo-controlled phase 2 study (NCT03675477). SHR0302 selectively inhibits JAK-1.The study started with an 8-week induction period followed by an 8 week long extension period. Patients with moderate to severe ulcerative colitis was included. This abstract presents the results for the 8-week-induction period. 164 adult patients were randomized to SHR0302 8 mg QD (once a day), 4 mg BID (twice a day), 4 mg QD or placebo. Clinical response at week 8 was the primary endpoint, defined as decrease from baseline in 9-point modified Mayo score (9mMS) of at least 2 and at least 30%, with an accompanying decrease in rectal bleeding subscore at least1 or absolute subscore of 0 or 1. Secondary endpoints were clinical remission and centrally read endoscopic remission.

Clinical response was achieved in all three active arms, compared to placebo. The percentage reaching clinical response was 46%, 46% and 44% for the different doses of SHR 0302, compared to 27% for placebo.

Clinical remission was achieved by 22%, 24% and 24% of the patients in the active arms and 5% in the placebo arm.

A Similar trend was observed for endoscopic remission with 26.8%, 29.3%, 36.6%, and 14.6% respectively.

Regarding safety, each treatment group (SHR0302 8mg QD, 4mg BID, 4mg QD, placebo) had 18 (43.9%), 20 (48.8%), 20 (48.8%) and 16 (39.0%) subjects experiencing at least one adverse event. The incidence of AEs across the three treatment groups was equal, but slightly higher than placebo group. There were no reports of death, PE, DVT, or major cardiac event in the study.

The authors concluded that SHR0302 significantly induced clinical response and clinical remission in patients with moderate to sever ulcerative colitis with a safety profile consistent with othe JAK-inhibitors.

(Reflection on page 5) ▶

REFLECTION

My reflection is that there are no data on the most important end-point, namely steroid-free clinical remission. Furthermore clinical remission, while on steroids or not, was achieved by only a minority of patients. Compared to the results for tofacitinib in the OCTAVE 1 and 2 induction studies, demonstrating clinical remission at 8 weeks in 18% and 16% respectively, SHR0302 seems to be at least as effective than tofacitinib although the differences are modest.

Outcomes of Tofacitinib Dose Reduction in Patients with Ulcerative Colitis in Stable Remission from the Randomised RIVETING Trial

Vermeire S, Su C, Lawendy N, Kobayashi T, Sandborn WJ, Rubin DT, Modesto I, Gardiner S, Kulisek N, Zhang H, Wang W, Panés J. Journal of Crohn's and Colitis 2021;15,(7):1130–1141.

The RIVETING trial is an ongoing double-blind randomized, parallel-group trial evaluating efficacy and safety of tofacitinib dose reduction to 5 mg twice daily versus 10 mg twice daily (BID). Patients in stable remission on tofacitinib 10 mg BID for more than six months while on tofacitinib for at least two years are included in the study.

The primary efficacy endpoint is remission based on modified Mayo score, please see the article for further explanation.

A total number of 140 patientes were randomized (1:1) to tofacitinib 5 mg or 10 mg BID. At six monts after randomization 77% and 90% of patients in the 5 mg and 10 mg BID groups respectively in remission. The adjusted difference was calculated to 12,9% (95% confidence interval 0.5-25.0).

Adverse events (AE) and serious adverse events (SAE) were similar in the treatment groups.

The authors conclude most patients in stable remission on 10 mg BID maintenance therapy maintained remission following dose de-escalation. In the group with de-escalation, patients in deep endoscopic remission and those without prior TNF-failure were more likely to maintain remission. Overall, 42.9% and 52.9% of the patients in the 5 mg and 10 mg groups respectively had been treated with TNF-inhibitors.

REFLECTION

My initial reflection is that more than two years treatment with the induction dose 10 mg twice daily differs from the way tofacitinib is used in Sweden. In the pharmacopoeia the length of induction therapy is recommended to between eight and 16 weeks. Perhaps similar results could have been obtained with an earlier dose de-escalation avoiding unneeded long time on the induction dose.

Current and future status of JAK inhibitors

McLornan DP, Pope JE, Gotlib J, Harrison CN. Lancet 2021;398:803–16.

I recommend this reviewarticle if You want to be updated on the theory behind JAK-inhibitors. Among other sections there is a section describing the results for tofacitinib, filgotinib and upadacitinib in treatment of inflammatory bowel disease. I also learned that there are additional JAK-inhibitors e peficitinib, ritlecitinib, brepocitinib, and TD-1473. As far as I can see, the compound SHR0302 has not yet been named.

Olamkicept, an IL-6 Trans-Signaling Inhibitor, is Effective for Induction of Response and Remission in A Randomized, Placebo-Controlled Trial in Moderate to Severe Ulcerative Colitis

Chen B, Zhang S, Wang B, Chen H, Li Y, Cao Q, Zhong J, Xie M, Ran Z, Tang T, Yang M, Guo T, Xu B, Cai Z, Ma L, Schreiber S, Chen M. Gastroenterology 2021;161(2):E28-E29.

Olamkicept is a compound that inhibits trans-signaling by binding to the IL-6/soluble IL-6R complex.

In this phase 2 multinational, randomized double-blind placebo-controlled trial, the effect of Olamkicept was evaluated in patients with moderate to severe ulcerative colitis. To be included the patients must have had an inadequate response to at least conventional therapy. Patients were randomized to olamkicept 300 mg or 600 mg or placebo, twice weekly for twelve weeks.

Clinical response was the primary endpoint. Mucosal healing and clinical remission was the secondary endpoints.

A total number of 91 patients were included and 88 completed the trial. Baseline disease and demographic characteristics were identical between the groups.

The share of patients reaching the primary endpoint, clinical response at week 12 was significantly greater for olamkicept 600 mg biweekly, 58.6 % compared to 34.5% for placebo. Clinical remission at week 12 was achived by none in the placebo group but 6.7% and 20.7% percent in the groups treated with 300 mg or 600 mg respectively.

Mucosal healing at wk 12 occurred in 3.4%, 10% and 34.5% ($P<0.001$) of patients, respectively. Adverse events was similar across the groups. The most common TEAEs included upper respiratory tract infection, increased AST levels, and increased urine bilirubin levels, all of which were mild to moderate and mostly transient. Serious adverse events were reported in 6.7%, 3.2% and 3.3% of patients, respectively. There were no deaths, or other severe Aes associated with pan-IL-6 inhibitors, such as GI perforations, severe infections, neutropenia or thrombocytopenia.

The authors concluded that biweekly olamkicept at 600 mg met both primary endpoint (response) and secondary endpoints (remission, mucosal healing). Olamkicept was well tolerated with a acceptable safety profile differing it from pan-IL-6 inhibitors. They claim that the positive results of this phase 2 study support further development of olamkicept in IBD.

REFLECTION

My reflection is first that the trial has a soft primary endpoint, clinical response. Our patients want remission and steroid-free remission in particular. All other outcomes must be regarded as a failure. Secondly, if steroid-free clinical remission is limited to around 20% in further clinical trials my opinion is that olamkicept has a limited value in treatment of ulcerative colitis.

Risankizumab Induction Therapy in Patients With Moderate-to-Severe Crohn's Disease with Intolerance Inadequate Response to Conventional and/or Biologic Therapy: Results from the Phase 3 ADVANCE Study

D'Haens GR, Colombel J-F, Bossuyt P, Danese S, Lim A, Lindsay J, Hisamatsu T, Ran Z, Rubin DT, Neimark E, Huang B, Liao X, Berg S, W. Duan R, Wallace K, Sandborn WJ. Gastroenterology 2021;161(2):E28.

Rizankizumab (RZB) ia monoclonacal antibody against interleukin-23, regarded as a key cytokine in the pathogenesis of inflammatory bowel disease. In phase 2 studies RZB has demonstrated both efficacy and safety for treatment of Crohns disease.
ADVANCE is a double-blind randomized phase 3 study evaluating efficacy and safety of RZB as induction therapy in patients with moderate to severe CD.

All patients included in the study had shown inadequate response (IR) or intolerance to previous biologic therapy (bio.IR) or to conventional therapy (non-bio-IR) The study has three arms RZB 600 mg, 1200 mg or placebo with 2:2:1 randomization, given at three occasions, week 0, week 4 and week 8.

Co-primary endpoints were clinical remission and endoscopic response at Week 12.
The primary intent-to-treat (ITT) population included 850 patients (non-bio-IR, n=360; bio-IR, N=490).

A significant higher number of patients in RZB 600 mg and 1200 mg dosing groups vs PBO (P<0.001) reached the co-primary endpoints (CDAI remission: 45.2% and 41.6% vs 25.2%; endoscopic response: 40.3% and 32.2% vs 12%). RZB showed efficacy regardless of biologic IR status by subgroup analysis. Furthermore, on-bio-IR patients had numerically higher rates of efficacy vs bio-IR patients.

Adverse event (AE) rates were similar in the RZB 600 mg and 1200 mg groups (56.3% and 51.3%) vs PBO (56.5%). Serious AEs (7.2% and 3.8% vs 15.1%), AEs leading to discontinuation of study drug (2.4% and 1.9% vs 7.5%), and serious infections (0.8% and 0.5% vs 3.8%) were numerically higher in the PBO group, due at least in part to AEs related to uncontrolled activity of CD (Table 2).Two deaths were reported in the PBO Group.

The authors conclude that rizankizumab 600 mg and 1200 mg was superior to placebo at inducing clinical remission and endoscopic response at Week 12 in patients with moderate to severe CD. Both rizankizumab doses were generally well-tolerated and AEs were consistent with the known safety profile of RZB.

REFLECTION

My reflection, with the risk of appear as nagging, is once again, it is not stated whether the clinical remisson was steroid-free or not. However, the proportion of patients reaching clinical remission is good enough.

Intravenous Ustekinumab Reinduction Is Effective in Prior Biologic Failure Crohn's Disease Patients Already on Every-4-Week Dosing

Sedano R, Guizzetti L, McDonald C, Jairath V. Clinical Gastroenterology and Hepatology 2021;19:1497–1498.

This article presents the results from a retrospective and prospective cohort study of realworld effectiveness outcome. Patients with moderate to severe Crohns disease with partial response or loss of response in spite of ongoing maintenance therapy with ustekinumab sc every fourth week were included in the study.
Patients were given an extra iv standard weight-based infusion dose and followed. A total number of 15 patients, two thirds were women. 80% of the patients were bio-exposed and 40% had failed two prior biologic compounds .Eight patients were on corticosteroids at reinduction.

Overall 13 patients responded to reinduction but one of them experienced loss of response at month 14 after reinducion. Patients were then followed up to a median time of 49 weeks after reinduction. At end of follow up, July 2020, 9 of 15 (60%) were still in remission.

The authors conclude that despite the small sample size, these data are useful to guide clinical practice, as it indicates that IV reinduction in patients already on maximal SC maintenance dosing is effective and safe and should be routinely attempted before prematurely switching out of class.

REFLECTION

My reflection is that it is obvious possible to get more from the drug even when the patient is on a quite intensive dose-regimen. There are unfortunately no data on serum concentration of ustekinumab, which of course is a weakness.

Paternal Exposure to Immunosuppressive and/or Biologic Agents and Birth Outcomes in Patients With Immune-Mediated Inflammatory Diseases

Meserve J, Luo J, Zhu W, Veeravalli N, Bandoli G, Chambers CD, Singh AG, Boland BS, Sandborn WJ, Mahadevan U, Singh S. Gastroenterology 2021;161:107–115.

This is a retroscpective cohort study. Study cohort 7453 expectant fathers with immune-mediated inflammatory diseases. Around the time of conception 461 were exposed to thiopurines, 171 to methotrexate, 1082 to TNF-inhibitors and 132 to non-TNF-targeting biologics. There were also a non-reported number of fathers on combination therapy with biologics and immunomodulators. 5607 of fathers were not exposed to any of the abovementioned compounds.
Primary outcome was the risk for congenital malformations. Other outcome measures were risk for preterm birth and low birth weight.

Compared to unexposed fathers (3.4% prevalence of congential malformations) exposure to thiopurines, methotrexate, TNF-α antagonists, or non-TNF-targeting biologics were not associated with increased risk for congenital malformations, preterm birth or low birth weight.

The authors conclude that immunosuppressive and/or biologic agents are safe to use in men planning conception.

(Reflection on page 9) ▶

▶ REFLECTION

My reflection is that this study add important data regarding the effect of paternal immune-mediated inflammatory diseases and requisite immunosuppressive medications on the offspring. Studies like this one are especially important, because pharmaceutical companies normally do not include pregnant women and men attempting to conceive in clinical trials.

Does Fatherhood Matter? Preconception Use of Biologics and Immunomodulators by Fathers With Immune-Mediated Diseases and Birth Outcomes of Their Offspring

Friedman S and Nørgård BM. Gastroenterology 2021;161:24-27.

An editorial linked up with the article above. Gives a good summary of the research on maternal use of biologics and immunomodulators during pregnancy and short-term birth outcomes.

Health outcomes of 1000 children born to mothers with inflammatory bowel disease in their first 5 years of life

Kanis SL,Modderman S, Escher JC, Erler N, Ruud Beukers R, de Boer N,Bodelier A et al on behalf of the initiative on Crohns and colitis. Gut 2021;70:1266–1274.

Design: A multicentre retrospective study in Netherlands. Women with inflammatory bowel disease who gave birth between 1999 and 2018 were included in the study. Information about disease characteristics, medication use, lifestyle, pregnancy outcomes and long-term health outcomes of children was retrieved from mothers and their medical charts.
After conscent of both parents outcomes for their children until the age of five wer collected from general practioners.

A total number of 1000 children born to 626 mothers (61% CD, 36% UC and 3% IBD-U).
In total 196 (20%) had intrauterine exposure to anti-TNFs (60 of them with concomitant thiopurine). 240 (24%) were exposed to thiopurine monotherapy. The remaining children, 564 (56%) not exposed to anti-TNF-α and/or thiopurine served as control group.

The new findings in this study are;

1. No association found between in utero exposure to anti-TNF-α and/or thiopurine and the outcomes antibiotic-treated infections and severe infections needing hospital admission.

2. No evidence for an association between exposure to anti-TNF-α and/or thiopurine during pregnancy and adverse reactions to vaccination, growth failure, autoimmunediseases and malignancies.

3. An association between thiopurine use during pregnancy and intrahepatic cholestasis of pregnancy without affecting birth outcomes and long-term health outcomes of children. How might it impact on clinical practice in the foreseeable future?

(Reflection on page 10) ▶

REFLECTION

My reflection; It is once again shown that anti TNFs and immunomodulators can be given during pregnancy without risks for the child. Another consoling finding is that the child to a mother with IBD does not seem to be at higher risk for infections, malignancies or autoimmune diseases. By the way, do the authors regard Crohns disease and ulcerative colitis as autoimmune diseases? As far as I can see the incidence of IBD among the children is not presented in the study. Does it mean that none of the 1000 children developed IBD during their first five years of life?

Lower Rates of Colorectal Cancer in Patients With Inflammatory Bowel Disease Using Anti-TNF Therapy

Alkhayyat M, Abureesh M, Gill A, Khoudari G, Saleh MA, Mansoor E, Regueiro M.

Chronic inflammation is regarded as a key factor for the development of colorectal cancer (CRC) in patients with IBD. The impact of bioglogic agents on colorectal carcinogenesis is unclear.

In this study used a multicenter database (Explorys) with electronic medical records from several US hospitals between the years 1999 to 2020. From this database a cohort of IBD was identified.

A total number of 62 007 510 patients between 1999 and 2020 were found in the database. Among them 225 090 had Crohns disease and 188 420 had ulcerative colitis. After adjusting for confounding factors patients with IBD were found to be more likely to develop CRC. In the IBD-group patients treated with anti-TNF agents were less likely to develop CRC. For patients with CD the odds ratio (OR) was 0.69 with a 95% confidence interval of 0.66-0.73. For patients with UC the OR was 0.78 with a 95% confidence interval of 0.73-0.83.

In addition there was found to be a statistically significant lower risk for CRC among those patients who received 5-ASAs. For patients with CD OR, 0.84 (95% CI, 0.81-0.87) and for patients with UC OR, 0.80; (95% CI, 0.77-0.83).

REFLECTION

My reflections; This is the first study studying the relationship between risk for CRC and use of anti-TNFs in patients with IBD. The risk is for CRC is found to be reduced in IBD-patients treated with anti-TNFs. The authors speculate about the explanation for the reduced risk. Is it reduced inflammation or inherent anti-carcinogenic effects of the compounds? The increased risk for certain other variants of malignancies with anti-TNFs speaks against the latter mechanism.
It is also interesting that new data on a possible protective effect of 5-ASAs is presented, both for UC and CD.

The Impact of Vedolizumab on Pre-Existing Extraintestinal Manifestations of Inflammatory Bowel Disease: A Multicenter Study

Ramos GP, Dimopoulos C, McDonald NM, Janssens LP, Hung KW, Proctor D, Elizabeth Ruggiero E, Kane S, Bruining DH, Faubion, WA, Raffals LE, Loftus Jr EV, Al-Bawardy B. Inflamm Bowel Dis 2021:27(8):1270-1276.

Design: A multicenter retrospective study of patients with IBD who has received at least one dose of vedolizumab (VDZ).

Primary outcome: Rate of worsening extraintestinal manifestations (EIMs) after initiation of VDZ. Secondary outcomes: factors associated with worsening EIMs and peripheral arthritis (PA) after VDZ.

A total of 201 patients with IBD were included in the study. Of them 72.6% had CD and 62.2% were female and the median age was 38.4 years. All patients had ongoing EIMs at the time of initiation of VDZ. The most common EIM was PA (68.2%). Worsening of EIMs after intitation of VDZ occurred in 34,8% of patients. There was no statistically significant differences between patients with worsened EIM (n = 70) and patients with stable EIM (n = 131) in terms of age, IBD subtype or previous and current medical therapy. PA was significantly more common in the worsening EIM group. Worsening of EIMs was associated with a higher rate of discontinuation of VDZ during follow-up when compared with the stable EIM group.

The authors conclude that one-third of patiens had worsening EIMs after initiation of VDZ, which resulted VDZ discontinuation in approximately 10% of patients.

REFLECTION

My reflection: It is not surprising that vedolizumab regarded as an intestinal-specific biologic agent has limited or no effect on extraintestinal manifestations in patients with IBD. However I don't think that the compound itself has an inherent negative effect. The lack of effect on, for example PA, is reasonably the explanation for the worsening seen.

Ustekinumab for Extra-intestinal Manifestations of Inflammatory Bowel Disease: A Systematic Literature Review

Guillo L, D'Amico F, Danese S, Peyrin-Biroulet L. Journal of Crohn's and Colitis, 2021, 1236–1243.

Design: Litterature search in PubMed, Cochrane Library and Web of Science up to October 2020 for all interventional and non-interventional studies published in English and assessing the efficacy of ustekinumab for treatment extraintestinal manifestations (EIMs).

Nine studies, eight retrospective and one prospective were included enrolling a total of 254 patients with IBD and EIMs.Ustekinumab was found to be effective for arthralgia and psoriatric arthritis in 152 patients. On the other hand, no effect was found in axial spondyloarthritis. Psoriasis, pyoderma gangrenosum and erythema nodosum were also responded to treatment with ustekinumab.

The authors concluded that ustekinumab showed to be an effective option for treatment of EIMs, in particular for dermatological and rheumatological manifestations with the reservation that more data are needed to confirm the role of in this setting.

(Reflection on page 12) ▶

REFLECTION

My reflections: I call in question that psoriatric arthritis and psoriasis are true EIMs in inflammatory bowel disease. Beside that it is not surprising that ustekinumab showed efficacy for treatment of psoriatric arthritis and psoriasis since the drug is approved for these diseases.

Complications and adverse effects related to surgical and medical treatment in patients with inflammatory bowel disease in a prospectively recruited population-based cohort

Rönnblom A, Ljunggren Ö, Karlbom U. Scand J Gastroenterol 2021. doi.org/10.1080/00365521.2021.1961309Raffals LE, Loftus Jr EV, Al-Bawardy B. Inflamm Bowel Dis 2021:27(8):1270-1276.

Design: A prospective population-based cohort followed for at least 10 years. All (n = 483) newly diagnosed patients with ulcerative colitis (n = 330) and Crohns disease (n = 153) in the county of Uppsala in Sweden between 2005 and 2009 were prospectively followed for ten years or until death.

In order to be classified as an adverse effect of the drug therapy, an incident severe enough to result in withdrawal of the drug must have occurred, not just a dose adjustment, with some degree of probability related to the action of a drug.

A total number of 122 (in the article the percentage is said to be 26.9%, but I calculate it to 25.2%) patients experienced one or more adverse effects during the pharmacological treatment. 25 of the adverse effectss could be classified as serious. For sulfasalazine (SASP) and immunomodulators, but not for mesalmine and biologicals, adverse effects occurred more often in patients with duration of IBD 17 years or more compared to duration less than 17 years. Fifty-seven malignancies were diagnosed during the observation time.

Adverse effects occurred more often in patients with CD (37.6%) compared to UC (20.3%). For the entire IBD-cohort the rate of adverse effects for the different treatments were as follows; steroids 3%, salicylates (other than SASP) 7%, biologics 24%, immunomodulators 25% and sulfasalazine (SASP) 26%.

Surgery was performed in 16 of 330 (4.8%) patients with UC and in 33 of 153 (22%) patients with CD. Frequency of early postoperative complications was 31% for UC patients and 36% for CD patients. The majority of complications were minor but two patients were re-operated, two needed intensive care and one patient died postoperatively.

The authors conclude that adverse effects related to medical therapy were experienced by approximately every fourth patient and by every third patient undergoing surgery.

REFLECTION

My immediate reflection is that this study has a narrow definition of adverse effects. In many cases patients experience adverse events, not necessarily caused by the drug but often resulting in dose adjustments. The overall impression is to some extent reduced by some small miscalculations.

Vedolizumab as first-line biological therapy in elderly patients and those with contraindications for anti-TNF therapy: a real-world, nationwide cohort of patients with inflammatory bowel diseases

Attauabi M, Höglund C, Fassov J, Pedersen KB, Bansholm Hansen H. Wildt S, Dam Jensen M, Neumann A, Cecilie Lind C, Albaek Jacobsen H, Popa A-M, Kjeldsen J, Pedersen N, Molazahi A, Haderslev K, Aalykke C, Knudsen T, Cebula W, Munkholm P, Bendtsen F, Seidelin JB, Burisch J. Scand J Gastroenterol 2021;56,(9):1040–1048.

Design: A Danish nationwide cohort study conducted between November 2014 and November 2019 who initiated treatment with vedolizumab mainly because contraindications to anti-TNF agents. A total number of 56 patients were included, 31 with UC and 25 with CD.

Primary outcome were clinical remission, steroid-free clinical remission and sustained remission from weeks 14 to 52.

For UC the rates of clinical remission was 32% week 6, 48% week 14 and 40% week 52. For CD the rates of clinical remission was 36.8% week 6, 36.8% week 14 and 47,4% week 52.
Steroid-free clinical remission at week 52 was achieved by 36% of UC patients and 47.4% of CD patients.
Sustained clinical remission was reached by 32% and 36.8% of UC and CD patients respectively.

Vedolizummab was well tolerated, with only one (UC) patient experienced a serious adverse event.

The authors conclude that vedolizumab is effective in the achievement of short-term, long-term and steroid free remission in bio-naïve patients with UC and CD.

REFLECTION

My reflection: The number of patients is small. The data were collected retrospectively and therefore some data are lacking, most obvious endoscopic findings.

The impact of body mass index on efficacy and safety in the tofacitinib OCTAVE ulcerative colitis clinical programme

Farraye FA, Qazi T, Kotze PG, Moore GT, Mundayat R, Lawendy N, Sharma PP, Judd DT. Aliment Pharmacol Ther. 2021;54:429–440.

The aim of this study was to assess efficacy and safety of tofacitinib in patients with ulcerative colitis, by baseline body mass index (BMI).

The authors performed a post hoc analysis evaluating patients with UC treated with either placebo och tofacitinib in OCTAVE Induction 1 and 2 studies and OCTAVE Sustain study.
Patients were stratified by their BMI at OCTAVE Induction 1 and 2 baseline in three strata; BMI < 25 or 25 <BMI> 30 or BMI ≥ 30.

Outcome measures were remission, endoscopic improvement, clinical response, sustained free remission, Inflammatory Bowel Disease Questionnaire total score and Short Form-36 Health Survey scores.

At Week 8 of OCTAVE Induction 1 and 2, and Week 52 of OCTAVE Sustain, higher proportions of patients receiving tofacitinib 5 or 10 mg twice daily (bid.) achieved clinical response vs placebo, regardless of baseline BMI subgroup (all $P < 0.05$).

There was no consistent trend between BMI and adverse events. Among patients receiving tofacitinib 10 mg bid. in OCTAVE Induction 1 and 2, serious infections were numerically greater in the BMI ≥30 subgroup (3.2%) vs other subgroups (0.4%).

The authors conclude tat efficacy and safety of tofacitinib were similar in patients with UC regardless of baseline BMI.

REFLECTION My reflection is that one size seems to fit all, at least in this study.