GUIDELINES AND CONSENSUS STATEMENTS

Second Mexican consensus on biologic therapy and small-molecule inhibitors in inflammatory bowel disease[☆]

J.K. Yamamoto-Furusho[a,*], F.J. Bosques-Padilla[b], M.A. Martínez-Vázquez[c], Working Group of the Second Mexican consensus on biologic therapy and small-molecule inhibitors[1]

[a] Clínica de Enfermedad Inflamatoria Intestinal, Departamento de Gastroenterología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[b] Departamento de Gastroenterología, Hospital Universitario de la Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico
[c] Hospital Zambrano Hellion TecSalud, Monterrey, Nuevo León, Mexico

Abstract
Introduction: Inflammatory bowel disease (IBD) is a chronic and incurable entity. Therapy with anti-TNF-α agents was the first biologic therapy approved in Mexico for IBD. New biologic agents, such as vedolizumab and ustekinumab, have recently been added, as have small-molecule inhibitors.
Aim: To update the biologic therapeutic approach to IBD in Mexico with new anti-TNF-α agents and novel biologics whose mechanisms of action induce and maintain remission of Crohn's disease and ulcerative colitis (UC).
Materials and methods: Mexican specialists in the areas of gastroenterology and inflammatory bowel disease were summoned to participate. The consensus was divided into 3 modules, with 49 statements. The Delphi method was applied, sending the statements to all participants to be analyzed and edited, before the face-to-face meeting. During said meeting, the clinical studies were shown, emphasizing the level of clinical evidence, and the final discussion and voting round on the level of agreement of all the statements was conducted.

Results: In this second Mexican consensus, recommendations are made for new anti-TNF-α agents, such as golimumab, new biologics with other mechanisms of action, such as vedolizumab and ustekinumab, as well as for the small-molecule inhibitor, tofacitinib.

Conclusions: The updated recommendations focus on patient-reported outcomes, biologic therapy, small-molecule inhibitors, and the safety aspects of each of the drugs.

Segundo Consenso Mexicano de Terapia Biológica y Moléculas Pequeñas en Enfermedad Inflamatoria Intestinal

Resumen

Antecedentes: La enfermedad inflamatoria intestinal (EII) es una entidad crónica e incurable. La terapia con agentes anti-TNF alfa fue la primera terapia biológica aprobada en México en EII. Recientemente han aparecido nuevos agentes biológicos como el vedolizumab y ustekinumab así como inhibidores de moléculas pequeñas.

Objetivo: Actualizar el enfoque terapéutico biológico de la EII en nuestro país con nuevos agentes anti-TNF alfa y nuevos mecanismos de acción para la inducción y mantenimiento de remisión de la enfermedad de Crohn y colitis ulcerosa crónica idiopática (CUCI).

Material y Métodos: Se invitaron a especialistas de la República Mexicana de las áreas de Gastroenterología y Enfermedad Inflamatoria Intestinal. Se dividió el consenso en 3 módulos, con 49 enunciados. Se aplicó el método de panel Delphi, para ello se envió las preguntas previó a la reunión a todos los participantes para que fueran editadas y ponderadas. Durante la reunión presencial se mostraron los estudios clínicos dando énfasis al nivel de evidencia clínica y se llevó a cabo la discusión y votación final del grado de acuerdo en todos los enunciados.

Resultados: Es el segundo consenso mexicano en donde se establecen las recomendaciones para nuevos anti-TNF alfa como el golimumab y otros mecanismos de acción como vedolizumab, ustekinumab y tofacitinib.

Conclusiones: Las recomendaciones actualizadas se centran en los resultados informados por los pacientes, la terapia biológica, los inhibidores de moléculas pequeñas y los aspectos de seguridad de cada uno.

Introduction

Inflammatory bowel disease (IBD) is an entity characterized by an inflammatory process in the gastrointestinal tract, with chronic alternating periods of relapse and remission, that includes ulcerative colitis (UC) and Crohn's disease (CD). Conventional treatment is with aminosalicylates (5-ASAs), topical steroids (budesonide), systemic steroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and immunosuppressants (cyclosporine, tacrolimus).[1]

Biologic therapy has been primarily based on anti-tumor necrosis factor-alpha (TNF- alpha) agents, which are the products most frequently utilized in Mexico, given that they are available in the public and private health sectors, and they include infliximab, adalimumab, certolizumab pegol, and golimumab. Anti-TNF-alpha-based biologic therapy is indicated for treating IBD that is moderate-to-severe or refractory or intolerant to conventional treatment.

Better understanding of the pathophysiology of the disease has enabled the development of new therapeutic alternatives focused on specific targets, such as: 1) anti-integrins (vedolizumab); 2) anti-interleukins 12 and 23 (ustekinumab), and 3) small-molecule Janus kinase (JAK) inhibitors.[2,3]

The present consensus deals with biologic therapy and small-molecule inhibitors and is an updated version of the Mexican consensus on the use of anti-TNF-alpha agents in the treatment of IBD that was published 10 years ago.[4] Since then, there have been important advances in the development and approval of more biologic agents for the treatment of IBD worldwide. In Mexico, other anti-TNF-alpha agents are available, such as golimumab, and biologics with different mechanisms of action, such as vedolizumab and ustekinumab, as well as the small-molecule inhibitor, tofacitinib.

Aim

To update the biologic therapeutic approach to IBD in Mexico with new anti-TNF-alpha agents and therapies with novel mechanisms of action to induce and maintain remission in CD and UC.

Methodology

The panelists were invited from all parts of Mexico, according to their career accomplishments and experience in the care of patients with CD and UC, in the areas of gastroenterology and IBD specialization. To organize this second consensus on biologic therapy and small-molecule inhibitors, the general coordinator, Dr. Jesús Kazuo Yamamoto Furusho, divided it into three modules that were distributed as follows:

- Module I. Patient-reported outcomes (PROs), Dr. Manuel Martínez Vázquez.
- Module II. Biologic therapy and small-molecule inhibitors, Dr. Jesús Kazuo Yamamoto Furusho.
- Module III. Safety aspects, Dr. Francisco Bosques Padilla.

Importantly, the remaining experts issued their votes and suggestions for each of the statements, based on the available scientific evidence.

A systematic search of the medical literature in English and Spanish was conducted for each statement formulated by the coordinators, utilizing Medline/PubMed, the Cochrane Database, EMBASE (Ovid), and LILACS. The search strategy included the following MeSH terms: Crohn's disease, ulcerative colitis, patient-reported outcomes, fecal calprotectin, remission, postoperative recurrence, biologic therapy, JAK inhibitors, anti-TNF-alpha, infliximab, adalimumab, certolizumab pegol, golimumab, vedolizumab, ustekinumab, tofacitinib, screening, opportunistic infections, tuberculosis, vaccination. All randomized clinical trials, meta-analyses, systematic reviews, cohort studies, and case-control studies published over the past 21 years (1998---2019) were included.

The working group of the second Mexican consensus on biologic therapy and small-molecule inhibitors was composed of 22 participants (gastroenterologists and IBD specialists). As stated above, the coordinators of each module were in charge of developing the initial statements and documenting the scientific evidence. The online platform, SurveyMonkey, was utilized to survey the participants and carry out statement modifications, with sponsorship by Takeda. The sponsor only provided financial support for the travel expenses of the members of the consensus working group and in no way influenced the content and development of the statements. In addition, none of the members received fees for their participation. An initial voting round, utilizing the Delphi method, was conducted on the electronic platform to observe the level of agreement of the

Table 1 Classification of the quality of evidence and strength of recommendations.[5]

Quality of evidence
High A
Moderate B
Low C
Very low D
Strength of recommendation
Strong, in favor of the intervention 1
Weak, in favor of the intervention 2
Weak, against the intervention 2
Strong, against the intervention 1

statements, as well as to make comments on specific references or suggest statement modification. The statements were voted on and the final modifications were carried out.

A face-to-face meeting was held in Mexico City, at which the 49 fin. l statements were accepted when > 75% of the participants voted 4 or 5 on a scale from 1 to 5.

The recommendations were based on the available level of evidence, according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) classification. The quality of evidence for each recommendation was classified as high, moderate, low, or very low, corresponding to the letters A, B, C, and D, respectively. Each recommendation was graded as strong (recommended), with the numeral 1, or weak (suggested), with the numeral 2, as shown in Table 1.[5] The strength of the recommendation is influenced by four aspects: risk/benefit balance; patient preference and values; resource availability; and quality of evidence. The final manuscript was drafted by the coordinators of each module and approved by all the consensus participants.

Module I. Patient-reported outcomes (PROs)

Statement 1. PROs have the potential to become a therapeutic goal in IBD. A variety of PROs have been utilized in clinical trials on IBD.

Agreement percentage: 100%. *Quality of evidence: B. Strength of recommendation: 2.*

Patient-reported outcomes (PROs) assess the result of treatment and healthcare regarding the disease. They are directly reported by the patient or caretaker and include thoughts, impressions, perceptions, and attitudes.[6,7]

Even though the best way to evaluate PROs is not standardized, the present consensus working group unanimously approved taking those measures into account, due to the growing bibliography on the topic and the worldwide trend to include the patient in the decision-making process, throughout the course of the disease. However, the quality of evidence is still insufficient for generalizing a specific measure.

The majority of the consensus participants accepted PROs as part of the measures to take into account, albeit they are not perfect for incorporating into clinical practice. To find their place in routine healthcare, PROs must be easy to use, acceptable to the patients and healthcare teams, and demonstrate an added value to normal practice, supporting decision-making at the level of individual patients.[8] Ideally, the same PROs should be used in clinical trials and practice, to prevent the current disconnect that occurs when interpreting clinical trial results and transposing them into routine clinical practice.

Statement 2. The quantitative measurement of fecal calprotectin is a noninvasive, safe, and reliable test, with good reproducibility.

Agreement percentage: 100%. *Quality of evidence*: A. *Strength of recommendation*: 1.

Fecal markers can be useful in the diagnosis of IBD and the monitoring of disease activity, as well as in treatment response. Up to 40% of patients present with mild inflammation, and other markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate, can be normal, limiting their utility in the follow-up of some cases.[9] Fecal calprotectin is a binding protein that is derived from neutrophils and plays a role in regulating inflammation. It is useful in differentiating IBD from irritable bowel syndrome (IBS).[10–12].

Statement 3. Treatment goals should be adapted to an individualized monitoring plan.

Agreement percentage: 100%. *Quality of evidence*: A. *Strength of recommendation*: 1.

In general, treatment goals have been based on fecal markers, serologic markers, and the use of endoscopy and magnetic resonance imaging. Due to the heterogeneity of the disease, each patient should be followed in relation to disease severity and activity, taking into account the basic principles of monitoring, which in certain cases can require a tight approach.[13,14]

Statement 4. Early therapeutic intervention improves deep remission (clinical and endoscopic) and prevents disease progression, complications, and disability, in early CD (less than 2 years of progression).

Agreement percentage: 100%. *Quality of evidence*: B. *Strength of recommendation*: 2.

The chronic intestinal inflammation that occurs in CD can lead to the intestinal complications of stricture, fistulas, and abscesses, often requiring surgical resections that can have severe consequences in relation to intestinal functional capacity. The factors associated with high risk for progression include young age at the time of diagnosis, the extension of intestinal involvement, ileal or ileocolonic involvement, rectal or perianal involvement, and the stricturing and fistulizing phenotypes.[15–17]

Statement 5. The goal in late CD is focused on stabilizing symptoms and limiting the progression of damage or disability, as well as improving quality of life.

Agreement percentage: 100%. *Quality of evidence*: A. *Strength of recommendation*: 1.

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program, initiated by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), examined potential treatment targets in IBD to be used for a ''treat-to-target'' clinical management strategy. Said strategy was determined through a process of evidence-based expert consensus.[18]

The group agreed upon 12 recommendations for UC and CD. The agreed target for UC was clinical PRO remission (defined as the resolution of rectal bleeding and diarrhea/altered bowel habit) and endoscopic remission (defined as an endoscopic subscore of 0-1).

Treatment based on the clinical risk for recurrence and approach through early colonoscopy, with intensive treatment for recurrence, is better than conventional pharmacologic treatment for the prevention of postoperative recurrence of CD.

Statement 6. Utilizing C-reactive protein (CRP), quantitative fecal calprotectin, and endoscopic monitoring is recommended because it optimizes anti-TNF-alpha treatment, resulting in a higher mucosal healing rate in IBD, compared with care that is based solely on symptoms.

Agreement percentage: 95%. *Quality of evidence*: A. *Strength of recommendation*: 1.

There is increasing evidence supporting a stricter approach to the patient in relation to biomarkers. In the CALM study, the effect of tight control management in CD was examined, reporting significantly better results than with symptom-driven decisions alone.[19] Tight control consisted of escalating therapy based on clinical findings evaluated through the Crohn's disease activity index (CDAI), taking into account elevated CRP and fecal calprotectin levels to optimize the biologic dose with adalimumab, which produced greater mucosal healing, compared with care that was based solely on symptoms.[19] The increase in treatment dose has not shown an increase in adverse effects or complications in the short term.

Statement 7. Treatment that focuses on the prevention of endoscopic recurrence in postoperative CD, with early colonoscopy (6 months) and intensive treatment, is superior to standard care.

Agreement percentage: 95%. *Quality of evidence*: A. *Strength of recommendation*: 1.

The majority of patients with CD require intestinal resection and the majority will later experience disease recurrence and need additional surgery. In a randomized trial that included 17 centers in Australia and New Zealand, the patients in whom endoscopic recurrence of CD was identified underwent intestinal resection through an endoscopically accessible anastomosis and received treatment with metronidazole for 3 months. Individuals at high risk for recurrence also received a thiopurine, or adalimumab, if they did not tolerate thiopurines. The patients were randomly assigned to parallel groups: colonoscopy at 6 months

(active care) or no colonoscopy (standard care). Complete mucosal healing was reached in 22% of the active care group versus 8% of the standard care group (p = 0.03).[20]

Statement 8. Quantitative fecal calprotectin levels can be a useful marker for monitoring postoperative recurrence of CD.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Anastomotic recurrence is frequent in CD after ileocecal resection. The degree of endoscopic recurrence, determined by the Rutgeerts score, is correlated with clinical and surgical recurrence. Several studies have demonstrated the diagnostic accuracy of fecal calprotectin for detecting endoscopic recurrence, but its optimal cutoff value has not yet been established. Fecal calprotectin is an accurate surrogate marker for postoperative endoscopic recurrence in CD. Its cutoff value of 150 µg/g appears to have the best general accuracy.[21] Serial monitoring of fecal calprotectin can eliminate or postpone the need for colonoscopic evaluation as postoperative recurrence surveillance in up to 70% of patients.

Module II. Biologic therapy and small-molecule inhibitors

Anti-TNF-alpha therapy

Statement 9. Serum biologic and TNF-alpha antibody measurement aids in identifying treatment response, based on mucosal healing, primary failure, or secondary loss of response.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Serum levels of infliximab above 3.5 µg/mL are associated with mucosal healing, defined as a Mayo score of 0 at week 30 in UC, enabling the development and validation of a clinical tool for deciding upon treatment optimization, according to the pharmacokinetic data of infliximab.[22]

Baert et al.[23] reported that serum levels >12 µg/mL correlated with longer response, compared with lower concentrations (p < 0.01). Those findings were confirmed by Maser et al.,[24] who found that higher infliximab levels were significantly predictive of endoscopic improvement, with an odds ratio (OR) of 23 and a 95% confidence interval (CI) of 4 to 124 (p < 0.001).

The quantification of serum levels of anti-TNF-alpha drugs and antibodies to anti-TNF-alpha drugs aids in understanding the mechanisms of loss of response, in optimizing the dose of the biologic, and in differentiating the patients that could benefit from the administration of biologics with different mechanisms of action.[25–27]

Increased serum levels of anti-infliximab antibody inversely correlated with drug response duration (p < 0.001).[23] Low doses of infliximab were also found to be significantly correlated with the presence of positive anti-infliximab antibodies, compared with the cases that

did not develop immunogenicity (p = 0.01).[28] Only 17% of patients with positive anti-infliximab antibodies responded to an increase in the dose of infliximab, compared with 86% of the patients with negative antibodies treated with suboptimal doses of infliximab that had clinical response upon increasing the dose of the drug (p < 0.01).[25]

Statement 10. Proactive drug monitoring with a treat-to-target approach can improve the efficacy, safety, and cost of anti-TNF-alpha therapy in IBD.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Adequate concentrations of serum anti-TNF-alpha levels have been associated with clinical and endoscopic remission. Low or undetectable anti-TNF-alpha levels have been related to increased risk for colectomy, secondary loss of efficacy, worse clinical outcomes, or increased inflammatory activity.[19,22–28]

Statement 11. The combination of infliximab and azathioprine improves the steroid-free clinical remission rate and mucosal healing, compared with monotherapy.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

The SONIC[29] study on CD showed that the combination of infliximab and azathioprine resulted in steroid-free clinical remission in 56.8% of the patients, compared with azathioprine as monotherapy (30%) at week 26, with statistical significance (p < 0.001), and compared with infliximab as monotherapy (44.4%, p = 0.02). Mucosal healing was significantly superior in the combination therapy group versus monotherapy with azathioprine (p < 0.001) and showed a trend toward significance versus monotherapy with infliximab (p = 0.06). In addition, the efficacy of the combination therapy of infliximab and azathioprine in UC was shown in the UC-SUCCESS clinical trial.[30] At week 16 there was a higher percentage of steroid-free clinical remission with the combination therapy, compared with monotherapy with azathioprine (p = 0.32) or with infliximab (p = 0.017), and mucosal healing was significantly better at week 16 in the combination therapy group, compared with the patients that received monotherapy with azathioprine (p = 0.001).

Statement 12. Therapeutic levels of anti-TNF-alpha are associated with better outcomes in children with IBD.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Proactive monitoring of serum levels of anti-TNF-alpha biologics and neutralizing antibodies to anti-TNF-alpha biologics in the pediatric population with IBD has shown favorable outcomes, such as steroid-free clinical and biochemical remission and overall wellbeing improvement in the children, maintaining optimal serum anti-TNF-alpha levels above 5 µg/mL.[31,32]

Statement 13. Biosimilar infliximab (CT-P13) therapy is effective for inducing and maintaining remission in IBD.

Agreement percentage: 100%. Quality of evidence: B. Strength of recommendation: 2.

In two systematic reviews with meta-analyses, biosimilar infliximab (CT-P13) has been shown to be efficacious and safe for the induction and maintenance of clinical remission in

UC and CD.[33,34] The Mexican Crohn's Disease and Ulcerative Colitis Academic and Research Group (*GAICCUM*, Spanish acronym) has also issued its position and recommendations on anti-TNF-alpha biosimilars in Mexico.[35]

Statement 14. Therapeutic levels of adalimumab are associated with endoscopic and histologic remission in IBD.

Agreement percentage: 100%. *Quality of evidence: B. Strength of recommendation: 2.*

Dose adjustment of adalimumab, based on serum levels of the biologic above 12 µg/mL, has been shown to be a factor associated with endoscopic and histologic remission in IBD (OR = 8; 95% CI: 2-31.9; p = 0.003).[36] When there are clinical and endoscopic signs of relapse, the quantification of serum levels of adalimumab and anti-adalimumab antibodies is recommended for dose optimization. Empirically doubling the dose or shortening the administration intervals have not been shown to improve clinical outcomes in CD or improve secondary loss of response.[37]

Statement 15. Adalimumab is more efficacious in patients with UC that are anti-TNF-alpha-naïve.

Agreement percentage: 100%. *Quality of evidence: A. Strength of recommendation: 1.*

The ULTRA 2 study evaluated the efficacy of adalimumab in the induction and maintenance of clinical remission in 494 patients with moderate-to-severe UC that were refractory to conventional treatment. The patients were divided into 2 groups: 1) adalimumab 160 mg week 0, 80 mg week 2, and 40 mg every two weeks up to week 52; and 2) placebo. In the adalimumab group, 22% of the patients that were anti-TNF-alpha-naïve achieved clinical remission at week 52, as did 12% of the patients in the placebo group (p = 0.029). Clinical remission was lower in the patients that previously received anti-TNF-alpha therapy, at 10.2% in the adalimumab group and 3% in the placebo group (p = 0.039). The efficacy of adalimumab was affected in the patients that had previous exposure to anti-TNF-alpha therapy.[38]

Statement 16. Increasing the dose of adalimumab improves secondary loss of response in IBD.

Agreement percentage: 100%. *Quality of evidence: B. Strength of recommendation: 2.*

Despite the standard dose of adalimumab, 30-40% of patients present with IBD activity in the first year of treatment. In CD, increasing the dose of adalimumab was successful in 67% of patients, 6 months after the optimization.[39] In contrast, in UC, dose escalation was required in 20-25% of patients the first year. The optimization success rate was 60% for regaining response in the UC patients that had secondary loss of response.[40]

Statement 17. Golimumab is effective for the induction and maintenance of clinical remission, endoscopic remission, and quality of life improvement in UC.

Agreement percentage: 100%. *Quality of evidence: A. Strength of recommendation: 1.*

Golimumab is a fully human IgG1 monoclonal antibody that is administered subcutaneously. Approved by the Food and Drug Administration (FDA) for the treatment of UC, its target is a unique epitope on the TNF-alpha molecule. It binds to both soluble TNF-alpha and transmembrane TNF-alpha, with the advantage that it has greater affinity for the soluble form than infliximab or adalimumab. Treatment response with golimumab has been reported in 54.9% of patients, with 45.1% achieving endoscopic remission at week 6. Regarding maintenance therapy, there was statistically significant response in 49.7% and endoscopic remission in 42.4%, compared with placebo, at week 54. Adverse effects were similar between groups. The number of studies is insufficient for issuing recommendations for combination therapy. However, concomitant use of immunomodulators is known to reduce immunogenicity but does not appear to affect their efficacy. Based on the existing evidence, we conclude that the use of golimumab as maintenance therapy every 4 weeks for up to 2 years is beneficial and enables reduced steroid use.[41,42]

Statement 18. Golimumab is effective as second-line treatment, in UC patients previously treated with an anti-TNF-alpha, but its efficacy is reduced when used as third-line therapy.

Agreement percentage: 100%. *Quality of evidence: B. Strength of recommendation: 2.*

In patients with UC that received golimumab as first, second, or third-line treatment, there was a statistically significant decrease in clinical response of 75%, 70%, and 50%, respectively (p = 0.007).[43] Therefore, golimumab is not recommended for use as third-line therapy.

Statement 19. A higher body mass index is associated with loss of response to anti-TNF-alpha agents and an increase in complications in IBD.

Agreement percentage: 100%. *Quality of evidence: B. Strength of recommendation: 2.*

In a cohort study on 180 cases of IBD treated with an anti-TNF-alpha agent, obesity was a factor associated with secondary loss of response in patients with UC (HR = 2.42; 95% CI: 1.03-5.70).[44] In a meta-analysis, obesity was associated with anti-TNF-alpha treatment failure in UC (OR = 1.413; 95% CI: 1.008-1.980; p = 0.045) but not in CD (OR = 1.099; 95% CI: 0.928-1.300).[45]

Vedolizumab

Statement 20. The administration of vedolizumab at an intravenous dose of 300 mg on weeks 0, 2, and 6, as induction therapy, and every 8 weeks, as maintenance therapy, is recommended.

Agreement percentage: 100%. *Quality of evidence: A. Strength of recommendation: 1.*

Vedolizumab (VLZ) is a humanized monoclonal antibody approved for the treatment of UC and CD and is administered intravenously. It recognizes the α4β7 heterodimer and selectively blocks leukocyte traffic. Its greatest advantage is that its highly selective mechanism of action restricts its immunosuppressive effects to the gut.[46] Despite advances in clinical experience, the mechanisms responsible for its efficacy are still being postulated and are the subject of intense research.[47]

Statement 21. Vedolizumab is efficacious for the induction and maintenance of lasting clinical remission, steroid-free remission, and mucosal healing in moderate-to-severe UC, even in anti-TNF-alpha-refractory patients.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

The GEMINI 1 is a randomized, double-blind, placebo-controlled study designed in separate induction and maintenance phases that was conducted at 211 hospitals in 34 countries. In the induction study, 374 patients (cohort 1) received vedolizumab 300 mg or placebo intravenously at weeks 0 and 2, and 521 patients (cohort 2) received vedolizumab at weeks 0 and 2, with disease evaluation at week 6. In the maintenance study, the responders to vedolizumab at week 6 from the two cohorts were randomly assigned to continue receiving vedolizumab every 4 or 8 weeks, or switch to placebo, for up to 52 weeks. Response was defined as a decrease of at least 3 points on the Mayo Clinic score (range: 0-12). Response rates at week 6 were 47.1% and 25.5% in the vedolizumab group and placebo group, respectively. At week 52, 41.8% of the patients that continued to receive vedolizumab every 8 weeks and 44.8% that continued to receive vedolizumab every 4 weeks had clinical remission (Mayo Clinic score $\leq$ 2, no subscore > 1), compared with 15.9% of the patients that switched to placebo. The frequency of adverse events was similar in the vedolizumab group and the placebo group. The GEMINI I study demonstrated the efficacy of vedolizumab for the induction and maintenance of remission in patients with moderate-to-severe UC that were refractory to conventional treatment and anti-TNF-alpha therapy. As maintenance therapy, there was statistically significant clinical remission in 41.8% of the patients with treatment every 8 weeks and in 44.8% with treatment every 4 weeks, compared with placebo.[48] Long-term treatment results in clinical improvement and better quality of life. Monthly doses are recommended for those patients that do not respond adequately to the conventional bimonthly dosing.[49]

Statement 22. Vedolizumab can be used as first-line therapy in patients with moderate-to-severe UC that are refractory to conventional treatment.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

The Latin American IBD treatment guidelines and the Mexican UC guidelines also recommend its use in UC as first-line treatment.[1,50]

Statement 23. The efficacy of vedolizumab for inducing response and clinical remission has been observed at week 10 in patients with moderate-to-severe CD that have had previous failure with an anti-TNF-alpha agent, and it is effective in response maintenance, lasting clinical remission, and steroid-free remission in patients with moderate-to-severe CD that are refractory or intolerant to conventional treatment and anti-TNF-alpha therapy.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

The GEMINI 2 study demonstrated the efficacy of vedolizumab in CD, with clinical remission achieved in 15% of the patients receiving vedolizumab, compared with 7% receiving placebo (p = 0.02), at week 6 of induction. In the maintenance phase (300 mg every 4 or 8 weeks), there was remission of CD at week 52 in 36% of the patients with treatment every 4 weeks (p = 0.004) and 39% of the patients with treatment every 8 weeks (p < 0.001), compared with 22% of the patients receiving placebo.[51]

The GEMINI 3 study evaluated the efficacy of vedolizumab in patients with moderate-to-severe CD that had failure to at least one anti-TNF-alpha drug. They were randomized to receive placebo or vedolizumab at a dose of 300 mg/day at weeks 0, 2, and 6. The primary outcome was clinical remission at week 6, and was achieved by 15.2% of the vedolizumab group, compared with 12.1% of the placebo group (p = 0.433). Clinical remission at week 10 was evaluated as the secondary outcome, resulting in a statistically significant difference between groups, with clinical remission in 26.6% of the vedolizumab group versus 12.1% of the placebo group (p = 0.001).[52]

Statement 24. Therapy with vedolizumab is optimized by shortening the infusion intervals from every 8 weeks to every 4 weeks, in patients that present with secondary failure or loss of response.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

The long-term clinical benefits of vedolizumab in CD are shown to continue, regardless of previous anti-TNF-alpha exposure, and that nonresponders to the conventional bimonthly dose of the biologic can benefit from the dose at shorter intervals.[53]

Statement 25. Treatment with vedolizumab is safe in IBD because it does not increase infectious or neoplastic processes. No case of progressive focal leukoencephalopathy has yet been reported.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

The main adverse effects that have been reported are nasopharyngitis, headache, arthralgias, and upper respiratory tract infections. The primary difference between natalizumab and vedolizumab is that natalizumab inhibits leukocyte traffic in multiple organs, including the brain, whereas vedolizumab acts specifically on gut-tropic $\alpha 4\beta 7$ heterodimers, thus selectively inhibiting lymphocyte traffic in the gut. At present, vedolizumab has shown no central nervous system complications, and because it is gut-selective, has no systemic effects, thus reducing adverse events.[49,51,52]

Statement 26. Intravenous and weight-adjusted administration of the first dose of ustekinumab is recommended, as is the subcutaneous administration of the maintenance dose of 90 mg every 8 or 12 weeks.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Ustekinumab is a fully human monoclonal antibody designed to bind to the p40 subunit common to interleukin (IL)-12 and IL-23. The binding of that antibody with the free fraction of IL-12 and IL-23 blocks the interaction of the IL-12 receptor (12Rß1) expressed in T cells, B cells, natural killer (NK) cells, macrophages, and dendritic cells.

Statement 27. Therapy with ustekinumab is efficacious in inducing and maintaining clinical response, clinical remission, and steroid-free remission in patients with moderate-to-severe IBD that are refractory to conventional and/or anti-TNF-alpha therapy. The optimization of therapy with ustekinumab is based on shortening the administration intervals of the subcutaneous 90 mg dose from 8 or 12 weeks to 4 or 6 weeks, respectively, in IBD patients that have loss of response or secondary failure.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Ustekinumab was evaluated in anti-TNF-alpha-refractory CD with moderate-to-severe activity. In the induction phase, 526 patients were randomly assigned to receive ustekinumab at intravenous doses of 1, 3, or 6 mg/kg, respectively, or placebo. In the maintenance phase, 145 of the patients with treatment response at 6 weeks randomly received subcutaneous injections of ustekinumab (90 mg) or placebo at weeks 8 and 16. There was clinical response at week 6 in 36.6%, 34.1%, and 39.7% of the patients that had doses of 1, 3, and 6 mg/kg of ustekinumab, respectively, compared with 23.5% of the patients that received placebo (p = 0.005 in the comparison with the group receiving 6 mg/kg). Maintenance therapy with ustekinumab, compared with placebo, significantly demonstrated clinical remission (41.7% vs 27.4%, p = 0.03) and clinical response (69.4% vs 42.5%, p < 0.001) at 22 weeks. Thus, ustekinumab use in anti-TNF-alpha-refractory CD of moderate-to-severe activity was effective, compared with placebo.[54]

There was clinical response at week 6 with ustekinumab in 34.3% of patients with moderate-to-severe CD and a history of failure with anti-TNF-alpha therapy. On the other hand, there was clinical response at week 6 in 55.5% of patients that were anti-TNF-alpha-naïve. Interestingly, ustekinumab showed rapid action onset from week 3 and clinical remission was maintained in 53.1% at week 44.[55,56]

In another randomized placebo-controlled clinical trial, 961 patients with moderate-to-severe UC treated with an initial 6 mg/kg infusion of ustekinumab, followed by 90 mg subcutaneously every 8 weeks or every 12 weeks, compared with placebo, were evaluated. At week 44, clinical remission was significantly superior in 43.8% of the patients that received ustekinumab every 12 weeks and 38.4% that received the drug every 8 weeks, compared with 24% that received placebo (p = 0.002 and p ≤ 0.001, respectively).[57] Administration every 8 weeks can be used as treatment optimization in cases of loss of response or secondary failure.

The initial dose is administered intravenously, according to patient weight. For patients that weigh < 55 kg, the dose is 260 mg of intravenous ustekinumab. In patients that weigh between 55 and 85 kg, the intravenous infusion dose is 390 mg, and in patients that weigh > 85 kg, 520 mg is administered intravenously, followed by 90 mg subcutaneously every 8 weeks, as maintenance therapy. The factors associated with response to ustekinumab in CD are female sex, young age at treatment onset, ileocolonic disease, and short disease duration (< 5 years). Previous anti-TNF-alpha

exposure appears to be associated with a slight decrease in the response rates to therapy with ustekinumab, compared with anti-TNF-alpha-naïve patients.

Statement 28. Treatment with ustekinumab is safe because it does not increase adverse events.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

The most frequent adverse effects are vomiting, nasopharyngitis, erythema at the injection site, vulvovaginal candidiasis, bronchitis, pruritus, urinary tract infections, and sinusitis.

Tofacitinib

Statement 29. The prescription of oral tofacitinib at a dose of 10 mg every 12 h for 8 weeks is recommended for inducing remission, and then 5 or 10 mg every 12 h as maintenance in UC.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Tofacitinib is the first selective inhibitor of the Janus kinase (JAK) family tested in humans. It has greater specificity for the JAK1 and JAK3 tyrosine kinases, which are involved in the signaling transduction of different interleukins (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), through stimulation of the gamma chain they share on the surface of the receptors for those interleukins, and are necessary for lymphocyte activation, function, and proliferation.[58]

Statement 30. Tofacitinib is efficacious in the induction and maintenance of remission and mucosal healing in patients with moderate-to-severe UC that are refractory to conventional and anti-TNF-alpha treatment.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

In a double-blind, placebo-controlled, phase II study, the efficacy of tofacitinib was evaluated in 194 adults with moderate-to-severe UC that were randomized to receive a dose of 0.5 mg, 3 mg, 10 mg, 15 mg, or placebo, twice a day, for 8 weeks. At week 8, clinical response was achieved in 32%, 48%, 61%, and 78% of the patients that received tofacitinib at doses of 0.5 mg (p = 0.39), 3 mg (p = 0.55), 10 mg (p = 0.10), and 15 mg (p < 0.001), respectively, compared with 42% with placebo. At week 8, there was clinical remission (defined as a Mayo score ≤ 2) in 13%, 33%, 48%, and 41% of the patients that received tofacitinib at doses of 0.5 mg (p = 0.76), 3 mg (p = 0.01), 10 mg (p < 0.001), and 15 mg (p < 0.001), respectively, compared with 10% of the placebo group.[59]

In a phase III study that evaluated remission induction with oral tofacitinib 10 mg, twice a day, for 8 weeks, clinical remission was achieved in 18.5% of the patients with UC. Clinical remission maintenance with 5 mg and 10 mg of tofacitinib was achieved in 34.3% and 40.6% of the patients, respectively, at week 52, whereas endoscopic remission was achieved in 6.7% of the patients receiving 10 mg of tofacitinib and only 1.6% with placebo, at week 8. Mucosal healing

was achieved in 31.3% of the patients receiving 10 mg of tofacitinib and only 15.6% of the patients given the placebo.

Statement 31. Tofacitinib does not significantly increase severe adverse events. However, the increase in the risk for developing herpes zoster must be kept in mind. Monitoring hemoglobin, lymphocyte, and neutrophil levels, as well as liver function tests and the lipid profile, is recommended during its administration.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

The most frequent adverse effects were headache, nasopharyngitis, arthralgias, and herpes zoster infection.[60] A recently published study on the safety of tofacitinib in moderate-to-severe UC, based on data from global clinical trials, reported the incidence rate (IR) for developing adverse events as follows: serious infections, IR = 2.0 (95% CI: 1.4-2.8); opportunistic infections, IR = 1.3 (95% CI: 0.8-2.0); herpes zoster infection, IR = 4.1 (95% CI: 3.1-5.2); malignancy (excluding nonmelanoma skin cancer), IR = 0.7 (95% CI: 0.3-1.2); major cardiovascular events, IR = 0.2 (95% CI: 0.1-0.6); and gastrointestinal perforation, IR = 0.2 (95% CI: 0.0-0.5).[61] Monitoring hemoglobin, lymphocyte, and neutrophil levels, as well as liver function tests and lipid profile, is recommended.

Module III. Safety aspects

Statement 32. All patients with IBD should be evaluated for hepatitis B virus (HBV) (HBsAg, anti-HBs, anti-HBc) at the time of IBD diagnosis to determine their HBV status. In HBsAg-positive patients, viremia (HBV DNA) should be quantified.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

IBD patients that have not been vaccinated against HBV should undergo the hepatitis B surface antigen (HBsAg) test, the antibody to the hepatitis B surface antigen (anti-HBs) test, and the IgG antibody to the hepatitis B core antigen (anti-HBc) test. If the serologic test is positive, a viremia quantification sensitivity test (HBV DNA) should be carried out. Patients with positive HBsAg or negative HBsAg and a positive anti-HBc result are at risk for HBV reactivation. For patients that are going to start immunosuppressive therapy, the use of prophylactics against HBV have shown an 87% relative risk reduction for experiencing reactivation (95% CI: 70-94%) and an 84% relative risk reduction for hepatitis flares.[62,63] Third-generation nucleoside or nucleotide analogue therapy is recommended over first and second-generation therapies because the first and second-generation drugs have a high resistance rate. Periodic monitoring of HBV DNA in seropositive patients after rescue therapy is left to the individual treating physician's criterion but the current literature recommends its performance every 3 months.[64,65]

Statement 33. At the time of IBD diagnosis, patients should be examined to evaluate whether they have already presented with primary varicella-zoster virus (VZV).

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Patients with no clear history of varicella, herpes zoster, or the administration of two vaccine doses for varicella should be evaluated for the presence of VZV IgG antibodies. Whenever possible, patients that are seronegative should complete the course of two doses of the varicella vaccine at least 3 weeks before starting immunosuppressive therapy. Subsequent immunization can only be carried out after a 3 to 6 -month suspension of all immunosuppressive therapy. All seronegative patients should receive timely prophylaxis after exposure.

VZV has been associated with an increase in the mortality rate in immunocompromised patients caused by various severe complications, such as pneumonia, disseminated varicella, encephalitis, or hemorrhagic conditions.[66] After acute VZV infection, the virus remains latent in the nervous system and can reactivate in the form of herpes zoster. Different studies have shown a relation between more severe manifestations of VZV and the use of anti-TNF-alpha agents.[67] An anti-TNF-alpha-related higher risk for developing VZV complications has been shown, with an OR of up to 3.29 (95% CI: 2.33-4.65), depending on the immunosuppressants employed. Therefore, susceptibility through the measurement of IgG antibodies to VZV should be carried out in all patients diagnosed with IBD.[68]

The European Crohn's and Colitis Organisation (ECCO) recommends vaccination in seronegative patients in two scenarios: 3 weeks prior to starting anti-TNF-alpha therapy and 3 to 6 months after the suspension of immunosuppressive therapy. According to the consensus of the Centers for Disease Control and Prevention (CDC) on the use of live attenuated vaccines against VZV in IBD and immunosuppression, vaccination is not contraindicated in patients that have a short-term steroid course, chronic use at a low dose (< 20 mg), methotrexate use, or thiopurine use.[69] If a high-risk IBD patient (immunosuppression or pregnancy) is seronegative for VZV and comes into contact with someone that has a VZV infection (varicella, disseminated varicella, varicella zoster), said patient should receive immunoglobulin-based prophylaxis against varicella zoster within 10 days after exposure and should be monitored for 28 days post-exposure, in addition to receiving therapy if there are clinical symptoms consistent with varicella.[67,68]

Statement 34. Routine prophylactic vaccination against human papillomavirus (HPV) is recommended for men and women, according to national guidelines. Prior or current HPV infection is not a contraindication for offering biologic therapy.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Human papillomavirus (HPV) has been associated with different types of cancer, such as cervical cancer, vulvar cancer, and vaginal cancer in women, penile cancer in men, and anal cancer and oropharyngeal cancer in men and women. It has been found to be a cause of precursor lesions in cancer, including intraepithelial cervical neoplasia and adenocarcinoma in situ.[70] There is a greater incidence of condylomata

or verrucous lesions associated with HPV in individuals undergoing immunosuppressive or biologic therapy.[71] HPV infection can be prevented by a conjugate vaccine but that does not eliminate the need for screening for the detection of cervical cancer.

Three prophylactic vaccines are available against high-risk HPV, to prevent HPV-related diseases: the quadrivalent, bivalent, and nonavalent. Our recommendation is to apply the nonavalent vaccine, given its greater coverage against different types of HPV. It is not clear whether the nonavalent vaccine in men substantially improves the prevention of penile cancer, but it indirectly reduces the risk for cervical cancer in women through herd immunity.[72] The application regimens in persons under 15 years of age are two doses, administered at month 0 and at month 6-12. Persons above 15 years of age or persons receiving immunosuppressants should receive three doses, administered at month 0, month 1-2, and month 6.[73,74]

Statement 35. Immunomodulator therapy is associated with a higher risk for developing severe influenza infection. Annual vaccination with the trivalent inactivated influenza vaccine or the quadrivalent recombinant influenza vaccine is an effective strategy for preventing influenza.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

Vaccination against the influenza virus is effective in immunocompromised individuals, achieving a laboratory-confirmed 85% reduction in infections, compared with placebo.[75] Influenza vaccination with the trivalent inactivated vaccine and the quadrivalent recombinant vaccine has been reported to be a safe and effective strategy for achieving protection against the influenza virus. It should be emphasized that the live attenuated influenza vaccine is contraindicated in IBD.[68,76]

Two phenomena that have made the use of the influenza vaccine inadequate have been described in the literature: suboptimal use of the vaccine in IBD and the presence of reduced immunogenicity in IBD. The former problem is improved through prevention with the use of the influenza vaccine, and for the latter, the suggestion is to apply the vaccine upon IBD diagnosis and yearly, regardless of immune status.[67] Administering a higher dose of the vaccine to patients undergoing anti-TNF-alpha therapy is also suggested, as it could improve immunogenicity and result in higher levels of post-immunization antibody titers.[77]

Statement 36. The prevention of *Pneumocystis jirovecii* pneumonia is recommended for patients on triple immunomodulators (a calcineurin inhibitor, steroids, or anti-TNF-alpha agent). Prophylaxis with co-trimoxazole should be considered for patients on double immunomodulators, especially if one of the drugs is a calcineurin inhibitor.

Agreement percentage: 100%. Quality of evidence: C. Strength of recommendation: 2.

Trimethoprim/sulfamethoxazole is recommended as primary prophylaxis for *Pneumocystis jirovecii* in patients that are receiving triple immunosuppressive therapy that includes systemic steroids, anti-TNF-alpha therapy, and calcineurin inhibitors in IBD. Primary prophylaxis for *Pneu-*

mocystis jirovecii in the IBD patient receiving double immunosuppressive therapy should be considered, especially if one of the drugs is a calcineurin inhibitor and the patient presents with a low albumin level.[78,79] The use of primary prophylaxis in IBD patients with pulmonary comorbidities, regardless of the immunosuppressive burden, is recommended.[80]

Statement 37. Regardless of the age of the patients receiving immunomodulator therapy for IBD, there is a risk for pneumococcal infection. Patients should undergo pneumococcal vaccination prior to immunomodulator administration.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

IBD patients have an increased risk for pneumonia, compared with the general population, with a risk rate of 1.54 (95% CI: 1.49-1.60). They also have an elevated risk for in-hospital pneumonia death.[81,82]

There are two vaccines on the market for preventing pneumococcus infection: the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13). Reports in the literature indicate that IBD patients receiving anti-TNF-alpha therapy have a diminished immune response to the PPSV23.[83] Persons receiving immunosuppressant therapy should receive a single dose of the PPSV23, followed by a booster every 5 years. In addition, one dose of the PCV13 should be administered >8 weeks before the PPSV23 or > 1 year after the PPSV23.[68]

Statement 38. IBD should not be a reason for restricting travel abroad. Individuals traveling to developing regions or endemic areas should have a medical consultation prior to the trip. Special consideration should be given to those receiving treatment with immunomodulators and biologics.

Agreement percentage: 100%. Quality of evidence: B. Strength of recommendation: 2.

Patients starting biologic therapy, with plans to travel to tropical areas (with a high prevalence of yellow fever, malaria, and others) should be examined in the travel medicine clinic, ideally by an infectious disease physician specializing in IBD, at least 4 weeks before traveling. Except for live attenuated vaccines, IBD patients should follow the same healthcare indications as non-immunocompromised persons. Travel destinations whose adverse living conditions are life-threatening, according to the gastroenterologist specialized in IBD, should be avoided.[84]

The vaccination records of individuals on immunomodulators and traveling abroad should be up to date, showing the dates of the vaccines applied and serologic evidence of immunity. Documentation of approved physical status from the healthcare provider should also be included.[68,81]

Statement 39. A standardized list adapted to local conditions is recommended for detecting the risk of opportunistic infection and should be filled out at the time of IBD diagnosis. The vaccination history should be reported at the time of diagnosis and the immunization status regularly updated. Live attenuated vaccines should be administered before beginning biologic therapy.

Agreement percentage: 100%. Quality of evidence: A. Strength of recommendation: 1.

A detailed clinical history with special emphasis on previous disease, medications of chronic use, and immunizations should be carried out. A standardized list of opportunistic infections and diseases that are relevant to IBD should be attached to the clinical history. Likewise, the vaccination history should be registered at the time of diagnosis, describing the vaccines that have been applied before starting immunomodulator therapy and determine immunization status through serology. The application of vaccines at the time of diagnosis and before starting immunomodulator and biologic therapy is recommended.[68]

Statement 40. There is a significant increase in infections in patients that take more than one drug, especially regarding the use of systemic steroids. Screening should be carried out for tuberculosis, hepatitis B virus, hepatitis C virus, HIV, and parasites (according to local epidemiology). Patients must be vaccinated before receiving immunomodulator therapy and/or biologic therapy.

Agreement percentage: 100%. Quality of evidence: B. Strength of recommendation: 2.

Among the studies that should be performed are complete blood count, liver function tests, blood chemistry, and serologic tests of certain infectious agents. Tests for diseases, such as tuberculosis, syphilis, and HIV, as well as IgG antibody testing for hepatitis A virus, hepatitis B virus, hepatitis C virus, and herpes simplex virus type 2, should be included. In addition, the presence of antibodies of the common herpes virus, such as Epstein-Barr, cytomegalovirus, herpes simplex type 1, and VVZ should be checked. In the absence of measles infection, the determination of IgG antibodies against measles should also be carried out.[67,84] Regarding the recommendations for opportune detection of parasitic infections before starting immunosuppressive therapy in IBD, no screening test for all parasitic disease is available, but avoiding the consumption of unsafe foods is mandatory.[67,85]

Statement 41. Anti-integrin molecules specific for the gastrointestinal tract (vedolizumab) have not shown an increased risk for opportunistic infections or neoplasias.

Agreement percentage: 100%. Quality of evidence: C. Strength of recommendation: 2.

The results of several studies have shown that vedolizumab use has not increased the risk for severe infections. Incidence rates of infection and serious infection were 63.5/100 person years and 4.3/100 person years, respectively, with vedolizumab, compared with 82.8/100 person years and 3.8/100 person years, respectively, with placebo. No opportunistic infections, such as disseminated tuberculosis, systemic candidiasis, disseminated herpes zoster, systemic cytomegalovirus infection, or *Pneumocystis* pneumonia were found in the medical literature. No cases related to the presence of progressive multifocal leukoencephalopathy have been reported in the rigorous monitoring of exposure to vedolizumab. Even though some immunosuppressive therapies in IBD have been described to be related to a higher incidence of skin cancer and lymphoma, the incidence of nonmelanoma skin cancer in patients exposed to vedolizumab has not been shown to be greater than that in patients receiving a placebo. Regarding lymphoma,

prospective studies documenting its risk with long-term use of vedolizumab are needed.[86,87]

Statement 42. Biologic therapy, including anti-TNF-alpha treatment, should be temporarily suspended in the presence of active infection and restarted once the infection has been eliminated.

Agreement percentage: 100%. Quality of evidence: B. Strength of recommendation: 2.

According to the most recent meta-analysis on the use of anti-TNF-alpha therapy, there is an increased risk for non-severe infections, but opportunistic infections are rare.[88] In real-world studies, septicemia and *Clostridioides difficile* infection are significant risk factors for having to discontinue and change medications in IBD treated with anti-TNF-alpha therapy.[89] The suspension of biologic therapy in the face of severe infection that compromises the hemodynamic status of the patient is recommended.

Statement 43. Screening for latent tuberculosis should be carried out before starting biologic therapy, including anti-TNF-alpha treatment. A dual strategy consisting of the traditional tuberculin skin test and the ELISA-based IGRA test is recommended for the baseline evaluation. Anti-tuberculosis therapy should be offered to patients with IBD that are diagnosed with latent tuberculosis, to reduce the risk of progression to active tuberculosis.

Agreement percentage: 100%. Quality of evidence: B. Strength of recommendation: 2.

Before starting anti-TNF-alpha therapy, the tuberculin skin test (TST) is insufficient for evaluating the evidence of latent *Mycobacterium tuberculosis* infection in an individual vaccinated with BCG, as occurs in Mexico, where the prevalence of tuberculosis is low. An ELISA-based IGRA test in immune-mediated inflammatory diseases has greater specificity than the TST and a low percentage of undetermined results. The QuantiFERON-TB Gold In-Tube or the T-SPOT.TB ELISA-based IGRA tests are employed to diagnose latent infection before starting anti-TNF-alpha therapy and neither of the tests is preferred over the other.

The TST cutoff point for starting preventive therapy against tuberculosis is ≥ 10 mm.[90] A TST with that cutoff point does not require confirmation by IGRA, and when there is a need to start anti-TNF-alpha therapy, prophylactic treatment should be given. Some authors recommend a double strategy that includes the sequential performance of the traditional TST test and an IGRA assay.[91]

In tuberculosis screening, when there is a positive TST and/or IGRA in the absence of clinical symptoms and a normal chest x-ray, latent tuberculosis is diagnosed. Starting biologic therapy, including anti-TNF-alpha treatment, at 4 weeks after the induction of preventive therapy against tuberculosis is recommended. Active tuberculosis is diagnosed when there are positive TST and/or IGRA tests and clinical symptoms, as well as chest x-ray findings, consistent with the disease. In cases of active tuberculosis, the suggestion is to refer to an infectious disease physician and start anti-TNF-alpha therapy after finishing the complete course of treatment against tuberculosis.[67]

Patients diagnosed with latent tuberculosis before starting anti-TNF-alpha therapy should be treated with a complete therapeutic regimen for latent tuberculosis. Treatment for tuberculosis should be given according to

the geographic zone and community-based epidemiology and the patient should be referred to an infectious disease physician. If the patient presents with active IBD and latent tuberculosis, anti-TNF-alpha therapy should be suspended for at least 3 weeks after starting anti-tuberculosis treatment, except in cases of clinical urgency and under the advice of a specialist. The duration of prophylactic treatment need not be lengthened in patients with latent tuberculosis that are receiving anti-TNF-alpha therapy.[67,84]

Statement 44. The optimal strategy for periodic evaluation should be every year in individuals with a history of latent tuberculosis or treated active tuberculosis.

Agreement percentage: 95%. *Quality of evidence*: C. *Strength of recommendation*: 2.

Based on the evidence available and the risk for new cases or reactivation of tuberculosis, yearly evaluation utilizing both the TST and IGRA tests for detecting the seroconversion of tuberculosis is recommended in patients receiving anti-TNF- alpha therapy. In patients on biologic therapy with anti-TNF-alpha agents, the TST cutoff point that should be taken into account is ≥ 5 mm.[90,92] High steroid doses can affect the result of the ELISA-based IGRA assay by giving an undetermined result.[93] Periodic evaluation aids in detecting new cases due to the increased risk for tuberculosis in patients receiving anti-TNF-alpha therapy.

Statement 45. Janus kinase (JAK) inhibitors are associated with an increased risk for infection, especially VZV, due to the direct suppression of critical components of the immune system.

Agreement percentage: 100%. *Quality of evidence*: C. *Strength of recommendation*: 2.

Tofacitinib is an orally administered molecule whose mechanism of action is the inhibition of the Janus kinase family. Its intracellular action can modulate the response of different cytokines involved in the pathogenesis of UC.[94] According to the existing literature on the treatment of IBD, the rates of any type of infection and of severe infections are higher in patients receiving treatment with JAK inhibitors. A higher rate of herpes zoster virus infection has also been reported.[60]

Statement 46. Screening for chronic HBV infection should be carried out before starting treatment with JAK inhibitors.

Agreement percentage: 100%. *Quality of evidence*: C. *Strength of recommendation*: 2.

Antiviral prophylaxis carried out in patients receiving a JAK inhibitor should be offered to those that are HBsAg-positive, to prevent HBV reactivation. In addition, the HBV viral load in patients that are anti-HBc-positive and HBsAg-negative should be monitored to evaluate the possible reactivation of occult HBV infection.

Prophylactic antiviral therapy and periodic HBV DNA monitoring are critical in chronic carriers that receive treatment with tofacitinib. Tofacitinib-based therapy appears to have a safe profile in patients with resolved HBV infections. In individuals with positive HBsAg and/or positive anti-HBc, HBV DNA should be quantified before starting systemic steroids, immunomodulators, or biologic agents. Antiviral therapy for the prophylaxis of HBV reactivation is recommended in individuals with detectable HBV DNA levels.[95,96]

Prophylaxis should be started 2 weeks before beginning immunomodulator therapy and should be continued for 6 to 12 months after discontinuing the immunomodulators. The clinician must be aware of the risk for reactivation in HBV carriers that do not receive prophylaxis with nucleotide analogues before starting JAK inhibition therapy.[95]

Statement 47. Screening for latent tuberculosis infection should be considered before starting treatment with JAK inhibitors, and then followed by the appropriate treatment, if necessary.

Agreement percentage: 100%. *Quality of evidence*: C. *Strength of recommendation*: 2.

Within a global program of patients that are being treated with tofacitinib, tuberculosis is the most frequent opportunistic infection. There is a higher relation between JAK inhibitor use and tuberculosis in countries with a high prevalence of the disease. Nevertheless, because many cases have a negative baseline screening test result, regular monitoring should be performed to opportunely detect latent tuberculosis, and those patients that are positive should be referred to a specialist for treatment with isoniazid.[97,98]

Statement 48. JAK inhibitors increase the risk for opportunistic infections (including tuberculosis, *Pneumocystis* pneumonia, herpes zoster, and fungi), especially in patients that have had previous or concomitant steroid use, a low lymphocyte count, or a high dose of JAK inhibitors.

Agreement percentage: 100%. *Quality of evidence*: C. *Strength of recommendation*: 2.

Tofacitinib has been associated with an increased risk for infections, including herpes zoster. In studies on JAK inhibitors, a higher serious infection rate has been found in the induction stage of those medications than in the maintenance stage. Likewise, a high prevalence of activation of opportunistic diseases, such as tuberculosis, has been described in relation to JAK inhibition therapy.[93,97] Up to a 3.83% probability of serious infection associated with maximum doses of JAK inhibitors has been found.[94]

Statement 49. Given the limited evidence available, the administration of antivirals and prophylactic drugs against *Pneumocystis* pneumonia should be individualized.

Agreement percentage: 100%. *Quality of evidence*: C. *Strength of recommendation*: 2.

Based on the existing evidence, prophylaxis against different viral diseases and against *Pneumocystis* pneumonia should be individualized, depending on the risk factors associated with the patient and his/her exposures to infectious agents. In some cases, prophylactic treatment of different infectious agents lacks consistency, but secondary prophylaxis is necessary in cases of prolonged immunosuppressive therapy and should be discussed with the appropriate specialist.[67]

In conclusion, this second Mexican consensus on biologic therapy includes updates in anti-TNF-alpha therapy and the mechanisms of action of novel anti-integrins, anti-interleukins, and small-molecule inhibitors, focusing on JAK inhibitors, such as tofacitinib.

Financial disclosure

Conflict of interest

Jesús Kazuo Yamamoto Furusho is a member of the advisory board, an opinion leader and speaker for Abbvie Laboratories de México, Abbvie (international), Takeda (international), Takeda México, Pfizer (international and regional), and Janssen Cilag (international and Mexico). He is an opinion leader and speaker for Farmasa, Ferring, and Farmasa Schwabe and a research advisor for UCB México. He has received funds for research studies from the Shire, Bristol Myers Squib, Pfizer, Takeda, and Celgene laboratories.

Francisco Bosques-Padilla. Speaker for Abbvie, Janssen, Takeda, and Ferring.

Manuel Martínez-Vázquez. Speaker for Abbvie, Janssen, and Takeda.

Working Group of the Second Mexican consensus on biologic therapy and small-molecule inhibitors in inflammatory bowel disease

Azucena Casanova Lara has been a speaker for Abbvie and Takeda.

Yolanda Cortés Aguilar has been a speaker for Abbvie.

Angel Ricardo Flores Rendón has been a speaker for Takeda.

Fabiola Maely González Ortiz has been a speaker for Abbvie.

Ylse Gutiérrez Grobe has been a speaker for Abbvie, Janssen, and Takeda

Gerardo López Gómez has been a speaker for Abbvie, Janssen, and Takeda.

Arturo Mayoral Zavala has been a speaker for Abbvie and Janssen.

Laura Ofelia Olivares Guzmán has been a speaker for Takeda.

The remaining authors have no conflict of interest.

Ethical considerations

No patients participated in the present study, nor were patient data described, thus obtaining informed consent was not required. Likewise, because no intervention, maneuver, or information management was involved, the study was considered low risk, requiring no review or approval by the local ethics committee. Nevertheless, it meets the current research regulations and guarantees identification and personal data confidentiality, as well as participant anonymity (all healthcare workers that voluntarily participated). The present article contains no personal information that could identify the participants.

Appendix A. Working Group of the Second Mexican consensus on biologic therapy and small-molecule inhibitors in inflammatory bowel disease

Emilio Fernando Bermúdez Villegas. HGR #25, IMSS, Mexico City, Mexico.

Azucena Casanova Lara. Hospital Regional del IMSS, Cancún, Mexico.

Armando Chevreuil Benítez. ISEM, Estado de México, Mexico.

Yolanda Cortés Aguilar ISSSTE. Guadalajara, Mexico.

Carlos Manuel del Real Calzada. Centro Médico Nacional La Raza, IMSS, Mexico City, Mexico.

Ángel Ricardo Flores Rendón. ISSSTECALI, Mexicali, Mexico.

Alejandro García Martínez. HGR #25, Mexico City, Mexico.

Fabiola Maely González Ortiz. Piedras Negras, Mexico.

Ylse Gutiérrez Grobe. Clínica de Enfermedad Inflamatoria Intestinal, Hospital General de México, Mexico City, Mexico.

Gerardo López Gómez. Clínica de Enfermedad Inflamatoria Intestinal, Centro Médico Nacional 20 de Noviembre, ISSSTE, Mexico City, Mexico.

Virgilio Marroquín Jiménez. Hospital de Especialidades del IMSS, Puebla, Mexico.

Arturo Mayoral Zavala. Centro Médico Nacional siglo XXI, IMSS, Mexico City, Mexico.

Laura Ofelia Olivares Guzmán. Hospital General de Culiacán, Sinaloa, Mexico.

Antonio Orozco Gamiz. Guadalajara, Mexico.

Azalia Ruiz Flores. Hospital de Alta Especialidad del IMSS, Monterrey, Mexico.

Alma Rosa Sánchez López. HGZ 2A Troncoso, Mexico City, Mexico.

Magdalena Sánchez Osorio. Hospital General de Tuxtla Gutiérrez, Chiapas, Mexico.

Fabiola Trejo Vázquez. ISSSTE Zacatecas, Mexico.

José Luis Vega Fonseca. ISSSTE, San Luis Potosí, Mexico

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