Utilizzo dei farmaci convenzionali nelle IBD: Gli statements IBD-Ahead

M Ferrante, K Karmiris, E Newnham, J Siffledeen, Z Zelinkova, G van Assche, PL Lakatos, J Panés, A Sturm, S Travis, CJ van der Woude, W Reinisch, J-F Colombel, R Panaccione. Physician perspectives on unresolved issues in the use of conventional therapy in Crohn's disease: Results from an international survey and discussion programme. Journal of Crohn's and Colitis 2012; 6:116–131.

Question 1: Introduction of corticosteroids

1. When should we introduce corticosteroids, and for how long?
   1. Systemic corticosteroids are best used for moderately to severely active Crohn's disease of any location. Their use in isolated perianal Crohn's disease is not supported.
   2. Budesonide is preferred to systemic corticosteroids for mildly to moderately active ileocaecal disease and right colonic disease, but is not universally available. In countries where budesonide is not available, early introduction of immunomodulators (and/or anti-TNF therapy) for their corticosteroid-sparing properties is appropriate.
   3. The duration of initial treatment with systemic corticosteroids at full dose depends on the response of the patient. There is no clear evidence that continuing the full dose (40–60 mg prednisone or equivalent) beyond weeks 1–3 influences remission rates. Patients who do not respond within 2–4 weeks had best be further investigated and other therapeutic options considered.

100% agreement after 2nd vote

Question 2: Dosing strategy for corticosteroids

2. What is the best dosing strategy for the use of corticosteroids, in terms of: starting and maximum doses, duration, dose escalation/de-escalation (when? rate?), formulation, avoiding side effects? What duration of corticosteroid treatment is linked to the occurrence of side effects?
   1. The optimal initial dose of oral systemic corticosteroids in Crohn's disease ranges from 40 to 60 mg/day to 1 mg/kg/day. For intravenous hydrocortisone, the optimal starting dose is 300–400 mg/day.
   2. The optimal starting dose of budesonide is 9 mg/day.
   3. Tapering of corticosteroids is generally initiated within a week of starting therapy, and after no more than 3–4 week There are no trials assessing different tapering regimens, and ‘standard’ regimens differ amongst centres. A reasonable approach is to reduce the dose by 5 mg/week, tapering to zero over 8 weeks (from an initial dose of 40 mg/day). Treatment should not exceed 12 weeks except in exceptional circumstances. Early introduction of immunomodulators or anti-TNF therapy is appropriate.
   4. No data are available to allow evaluation of any benefit of intentional dose escalation of corticosteroids.
   5. Systemic corticosteroids and budesonide are ineffective as maintenance therapy. It is strongly recommended to taper all corticosteroids to zero and switch appropriate patients to immunomodulator (or anti-TNF) therapy.
   6. Corticosteroids have been shown to increase the risk of serious, opportunistic infections and mortality, both independently or in combination with immunomodulators and anti-TNF agents.
   7. The best way to prevent corticosteroid-induced side effects is to avoid prolonged or repetitive use and to switch appropriate patients to immunomodulator therapy and/or anti-TNF therapy. Surgery is an appropriate option for some patients demonstrating corticosteroid dependency and could be considered.
   8. To prevent corticosteroid-induced loss of bone mineral density, calcium and vitamin D supplements should be provided. Clinicians treating with corticosteroids should familiarise themselves with local guidelines in managing corticosteroid-induced metabolic bone disease.
   9. Not all corticosteroid-induced side effects occur dose- or time-dependently.

94% agreement after 2nd vote

Question 3: Introduction of immunomodulators

3. How early should immunomodulators be introduced and which regimen should be used?
   1. Initiation of immunomodulators (±anti-TNF therapy) early in the disease course (often within a week or two of diagnosis) should be considered for patients with severe disease, paediatric patients and for patients at high risk of progression to disabling disease.
   2. It is generally appropriate to start thiopurines or methotrexate in immunomodulator-naïve patients who have a relapse, are corticosteroid-dependent, or who need repeated courses of corticosteroids. This may include patients who need two or more courses of corticosteroids within 12 months; who relapse as the corticosteroid dose is tapered below 15 mg; or who relapse within 3 months of stopping corticosteroids. These limits are arbitrary, but serve as guidance for clinical practice. The aim is to withdraw corticosteroids completely.
   3. Thiopurines are currently indicated for postoperative prophylaxis immediately after surgical resection of ileocolonic disease. This is true in patients with high risk of recurrence; in the other patients thiopurines should be introduced if there is evidence of recurrence at 6–12 months.

89% agreement after 2nd vote

Question 4: Dosing strategy for immunomodulators

4. What is the best dosing strategy for immunomodulators, in terms of: starting and maximum doses, duration, dose escalation/de-escalation (when? rate?), which immunomodulator first?
   1. The most effective doses appear to be 2.0–3.0 mg/kg/day for azathioprine and 1.0–1.5 mg/kg/day for mercaptopurine. Initial dose strategies in common practice are either a gradual dose increase starting with 50 mg parenteral azathioprine (25 mg mercaptopurine) or full dose therapy with prior determination of thiopurine methyltransferase (TPMT) activity/genotype.
   2. For methotrexate, the dosing strategy best supported by evidence from clinical trials is 25 mg per week for 8–12 weeks and 15 mg per week for maintenance.
   3. Azathioprine is generally used as a first-line immunomodulator.
   4. Azathioprine/mercaptopurine treatment is best maintained for several years because of the high relapse rates in patients with Crohn's disease when these drugs are discontinued.

93% agreement after 2nd vote

Question 5i: Monitoring efficacy

5(i). How should efficacy of a treatment be monitored clinically and biologically? What is the definition of treatment failure? When should the effect of treatment be evaluated?
   1. Assess remission status/treatment success using clinical signs and symptoms together with normal biological markers (CRP, faecal calprotectin). Endoscopy and imaging techniques can also be used to determine inflammation objectively or when response to treatment is unclear. The CDAI and Harvey Bradshaw Index can be used to quantify clinical efficacy, although opinion differs regarding the relative utility of these tools in everyday practice.
   2. Assessment of azathioprine metabolite levels is useful in making management decisions and to identify non-compliant patients or assess non-responders.
   3. Trough levels of anti-TNF agents may be useful for identifying the cause of non-response.
   4. Treatment failure may be defined after the appropriate period of therapy as:
      i. Lack of symptomatic response
      ii. Lack of improvements in biological markers
      iii. Lack of corticosteroid-free remission
      iv. Inflammation, signs of mucosal ulceration with endoscopy or imaging
   5. Clinical response/treatment failure should be assessed at:
      i. Thiopurines or methotrexate: not earlier than 3 months, not later than a maximum period of 6 months
      ii. Anti-TNFs: at a maximumperiod of 14 weeks (6–14 weeks) after starting therapy
      iii. If mucosal healing is to be assessed, this should be performed between 6 and 12 months

79% agreement after 1st vote

Question 5ii: Assessment of mucosal healing

5(ii). Should mucosal healing be assessed?

1. In the absence of a clinical indication, there is insufficient evidence to recommend the routine assessment of mucosal healing in clinical practice. The assessment of mucosal healing may have a useful role in guiding treatment adjustments.

85% agreement after 1st vote

Question 6: Combination of azathioprine and an anti-TNF agent

6. If azathioprine and an anti-TNF agent are given in combination, should any of the treatment be stopped? Which treatment should be stopped to achieve the smallest reduction in efficacy? When should that treatment be stopped?

1. When using azathioprine with anti-TNF therapy, the immunomodulator treatment must be individualised according to the individual's treatment and disease status. The benefits of long-term therapy must be weighed against the potential risks for each patient:

i. If the patient hasmoderately active Crohn's disease and is naïve to immunomodulator therapy, the combination of immunomodulator and infliximab can improve rates of corticosteroid-free remission for up to 1 year

ii. In a patient flaring despite immunomodulator therapy, maintaining the combination of immunomodulator and anti-TNF therapy beyond 6 months may offer no clinical benefit, although this is disputable

iii. There is an increased risk of opportunistic infection with long-term immunomodulator and anti-TNF therapy and of malignancy with thiopurine therapy

iv. There is a small potential risk of hepatosplenic T cell lymphoma (HSTCL) in young adults, particularly young males, with a combination of azathioprine and infliximab or adalimumab

86% agreement after 2nd vote

Question 7: Immunomodulator failure

7. If the immunomodulator does not work, what should the approach be? Increase the dosage? Add corticosteroids? Change the immunomodulator? Move to an anti-TNF agent?

1. In any patient with a flare or symptoms rule out infections and complications.

2. In a patient on standard weight-based dose of thiopurines there is no evidence for dose increase.

3. Anti-TNF therapy can be the first consideration in patients who have been on optimal immunomodulator therapy and lost response.

4. If a patient shows intolerance or side effects to purine metabolite immunomodulators, other immunomodulators (methotrexate) or anti-TNF agents may be considered.

83% agreement after 2nd vote

Question 8: Flare-ups with immunomodulators or anti-TNFs

8. If a patient experiences flare-ups when receiving immunomodulators or anti-TNF therapy, should corticosteroids be added?

1. If a patient loses response to an anti-TNF agent, optimisation of therapy should be considered before starting corticosteroids

i. It is necessary to re-evaluate disease and confirm inflammatory disease before optimising therapy

2. If a patient loses response to immunomodulator therapy, optimisation of therapy and checking compliance should be considered before considering corticosteroids. Avoid use of corticosteroids when failing immunomodulator therapy where possible

i. Switching to an anti-TNF does not usually require bridging corticosteroids

ii. If corticosteroids are necessary (e.g. to switch between immunomodulator therapies) dose should be tapered over a period of weeks to limit exposure to their significant side effects

77% agreement after 1st vote

Question 9: Risk of cancer and infection

9. What are the risks of cancers (all kinds) and infections associated with the short-, mid- and long-term use of immunomodulators and corticosteroids?
   1. Although absolute risk is very low, combined use of thiopurines and anti-TNF agents increase the risk of lymphoproliferative disorders.
   2. The risk of other malignancies (solid organ tumours) associated with thiopurines and combined thiopurine and anti-TNF therapy still needs to be proven, although there is an increased risk of non-melanoma skin cancer and yearly skin examination should be routinely practised.
   3. In most cases, the absolute risk of malignancy remains low; however, the impact of additional risk factors such as young age, Epstein Barr virus status, older age (N65 years), malnutrition, and history of previous malignancy should be taken into account.
   4. Immunomodulators and/or corticosteroids and anti-TNF agents are associated with an increased risk of infection. Long-term corticosteroids, but not other immunomodulators, appear to increase risk of perioperative infection. The risk of infection is further increased in older patients, and in patients with co-morbidities and/or malnutrition.
   5. The risk of infection in patients with IBD is likely to increase with the number of immunomodulator agents that are used concomitantly, particularly with use of concomitant corticosteroids.
   6. The long-term concomitant use of thiopurine and anti-TNF therapy should be carefully considered. In adolescents and young (b35 years) patients (particularly males), combined thiopurine and anti-TNF therapy should be used with caution because of the small risk of HSTCL.

90% agreement after 1st vote

Question 10: Optimal safety monitoring

10. What is the optimal safety monitoring (clinical, laboratory, radiological) of patients receiving immunomodulators or corticosteroids? How often?
   1. There may be severe myelosuppression in all patients receiving immunomodulator therapy
      i. TPMT analysis (where readily available) may identify those with low TPMT activity at greatest risk of severe haematological complications
      ii. Also consider a gradual dose increase starting with 1 mg/kg azathioprine (0.5 mg/kg mercaptopurine), with regular (1–2 weekly) blood count monitoring until target dose is achieved
      iii. Patients should be informed about the risks (including pancreatitis) and proper diagnostic steps should be performed when appropriate
   2. In addition to clinical safety monitoring, carry out regular monitoring of full blood count and liver function tests in all patients receiving thiopurines and methotrexate. For example, before initiating therapy, every 1–2 weeks during the first month, monthly up to 3 months, and then every 3 months
      i. In patients with persistently elevated liver function tests under methotrexate therapy, methotrexate should be stopped and liver biopsy considered (American College of Rheumatology guidelines)
   3. In addition, take the following measures in patients initiating or taking immunomodulators:
      i. Follow guidelines for the prevention of opportunistic infections in IBD (e.g. ECCO consensus and US guidelines)
      − Vaccinations
      − Pap smear for females receiving thiopurines
      ii. Solar protection for patients receiving thiopurines, including regular dermatological screening for long-term thiopurine use
      iii. Seek urgent medical advice for clinical signs of fever, severe infections, unexplained symptoms, including neurological
   4. Patients receiving high doses of corticosteroids should also undergo clinical monitoring, paying particular attention to the risk of opportunistic infection, intra-abdominal abscesses, perforations, hypertension, diabetes (or worsening diabetes) and ophthalmological complications (glaucoma)
      i. There is no evidence to support a particular method of monitoring
      ii. Calcium and vitamin D supplementation should be considered

97% agreement after 2nd vote