ORIGINAL ARTICLE

Role of biological therapy for inflammatory bowel disease in developing countries

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Revised 29 July 2011
Accepted 2 August 2011
Published Online First 13 October 2011

ABSTRACT

Inflammatory bowel disease (IBD) has become a global disease. Its incidence in developing countries is rising. In Asia, this has been attributed to the rapid modernisation and westernisation of the population. As IBD emerges in developing nations, there is a need to reconcile the most appropriate treatment for these patient populations from the perspectives of both disease presentation and cost. In the West, biological agents are the fastest-growing segment of the prescription drug market. They typically cost several thousand to several tens of thousands of dollars per patient per year. The healthcare systems in developing countries will struggle to afford such expensive treatments. Developing countries cover two-thirds of the earth's surface and are home to 3—5 billion inhabitants, constituting three-quarters of all humanity. If IBD emerges to the same extent in those countries as it has in the West, the need for biological therapy will increase dramatically, and the pharmaceutical industry, healthcare providers, patient advocate groups, governments and non-governmental organisations will have to discuss how to handle this. The authors propose that this dialogue should begin now with regard to (1) the major needs of patients with complicated IBD in developing countries, (2) the potential need for biological therapy in developing countries to treat IBD, (3) the necessary infrastructure for selecting patients with IBD who need biological therapy, and (4) medical/ethical issues limiting the use of biological therapy.

Significance of this study

What is already known about this subject?

- The incidence of inflammatory bowel disease (IBD) (especially ulcerative colitis) is rising in developing countries.
- Complicated disease courses that would profit from anti-tumour necrosis factor (TNF) therapies will therefore increase in number.
- The problem of the limited availability of anti-TNF in developing countries has never been discussed in detail.

What are the new findings?

- The emerging issue of medical support for severely ill patients with IBD in developing countries is discussed for the first time.
- A discussion is initiated to answer the question as to how to support severely ill patients with IBD in developing countries.
- A dialogue is suggested as to how experience with anti-TNF agents in the West can be transferred most efficiently from countries with high availability to countries with so far very limited availability.
- Ethical issues on the limited availability of anti-TNF in developing countries are discussed.

How might it impact on clinical practice in the foreseeable future?

- The initiation of a discussion should lead to joint actions of health officials in the developing world, IBD experts, the WHO and the World Gastroenterology Organisation.

INTRODUCTION

Inflammatory bowel disease (IBD) has long been considered a problem of the Western world, with a Western lifestyle contributing to the pathogenesis. IBD now is a global disease (figure 1).[1 2] Its incidence in developing countries is rising. In Asia, this has been attributed to the rapid modernisation and westernisation of the population.[2]

As IBD emerges in developing nations, there is a need to reconcile the most appropriate treatment for these patient populations from the perspective of both disease presentation and cost. In the West (USA, Canada, Europe, Australia), biological agents are the fastest growing segment of the prescription drug market. It is projected that they will account for 50% of all new drugs approved by 2014.[3] For IBD therapy, infliximab and adalimumab have been approved in North America including Mexico, Australia and Western Europe, certolizumab pegol has been approved in the USA and Switzerland, and natalizumab in the USA. Several new biological agents are under study or in the middle of the approval process. Typically, biological agents cost several thousand to several tens of thousands of dollars per patient per year. The cost per year for a patient on scheduled, continuous maintenance treatment with anti-tumour necrosis factor (TNF) is at least ~US$20 000.

The healthcare systems in developing countries will have difficulty affording such expensive treatments. Developing countries cover two-thirds of the earth's surface and are home to 3-5 billion inhabitants, constituting three-quarters of all humanity. If the increase in IBD incidence and prevalence is similar in these countries to the experience in the West in the 1970s and 1980s, the need for biological therapy will expand

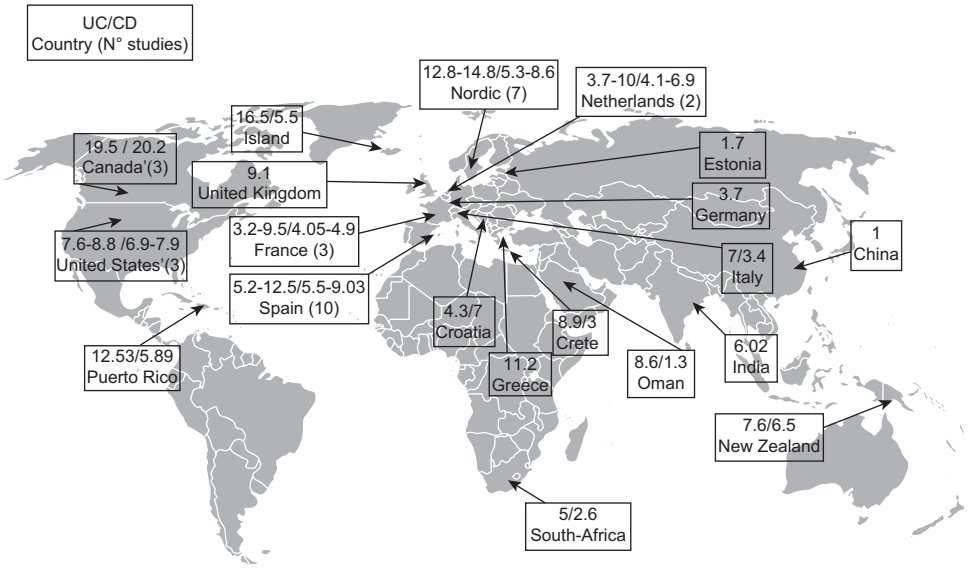

Figure 1 Incidence of Crohn's disease (CD) and ulcerative colitis (UC) worldwide (according to Goh and Xiao[2]).

dramatically. The demand for sufficient therapy for patients with severe IBD will then force the pharmaceutical industry, healthcare providers, patient advocate groups, governments and non-governmental organisations into a dialogue about how to handle this dilemma. However, starting this dialogue when demand has already caused conflict and major problems may be too late. We therefore propose that it should be initiated now. The discussion should cover several important aspects. The major needs of patients with complicated IBD in developing countries should be analysed. The potential need for biological therapy to treat IBD in developing countries should be explored. The necessary infrastructure for selecting patients who need biological therapy should be evaluated, and medical/ethical issues limiting the use of biological therapy need to be addressed. Based on these assumptions, this paper is intended to raise awareness of the issue of biological therapy in developing nations and to initiate this dialogue.

IBD IN DEVELOPING COUNTRIES: AN INCREASING MEDICAL PROBLEM

The incidence of ulcerative colitis (UC) increased in Western countries in the 1960s and 1970s, and then plateaued. In contrast, the incidence of UC is clearly increasing in previously low-incidence areas in Eastern Europe, Asia and developing countries.[4 5] The incidence of Crohn's disease (CD) is high in Canada and New Zealand, intermediate in Western Europe and the USA, and lower in Israel and South Africa. Although rates are low, it seems to be rising in Asia and South America.[2 6–9]

In developed countries, UC emerged first and then CD followed. However, in the past 20 years, CD has generally matched or overtaken UC in incidence and certainly has overtaken UC in prevalence in most Western nations except Scandinavia.[10] In developing nations where IBD is emerging, UC typically is more common than CD. In India for example, there are reports of a UC/CD ratio of 8:1.[2 11] There is a continuing trend of increasing incidence and prevalence of IBD across Asia (in particular in East Asia). Although this emergence is occurring among developing nations, it is also occurring in Japan, an advanced country from a socioeconomic perspective.

Nevertheless, it is potentially an important aetiological clue that UC is much more common than CD in developing countries. From the perspective of biological therapy, these drugs are used more often to treat CD. On the basis of current evidence, the percentage of patients potentially suited for biological treatment is much lower in these developing countries.

CD TREATMENT NEEDS

The primary aim of treatment of both UC and CD is to induce and maintain remission, as well as to prevent relapse. IBD management in the West typically requires long-term treatment usually with a combination of drugs. The optimal goal is to maintain corticosteroid-free remission and prevent complications, hospitalisation and surgery. Of course, these general treatment aims are the same in Western and developing countries. Worldwide, a large number of patients with CD receive 5-aminosalicylic acid (5-ASA) preparations[12] despite meta-analyses that suggest no, or low, efficacy of these agents for acute CD.[13] In the pre-biological therapy era, Faubion and coworkers showed that, in a cohort from Olmsted County, Minnesota, 43% of patients with CD were treated with corticosteroids.[14] This means that more than 50% of the patients did not require corticosteroid treatment (figure 2). In this cohort, more than one-third of patients came into remission with a less intense treatment with fewer side effects that did not require monitoring. In acute flares of CD, corticosteroids are still highly effective for achieving remission.[15–17] Remission is achieved in at least 60%, leaving ~ 40% who need other treatments.[18] In the Olmsted County Study, 32% of patients with CD were corticosteroid free without operation at 1 year.[14] So most patients require something other than corticosteroid therapy to induce or maintain remission, whereas some require little or no therapy after corticosteroid induction. It is critical to discern predictors of which patients may require long-term immunosuppressive therapy versus those who do not.[6] However, it would seem that, in countries with fewer resources, less expensive treatments such as corticosteroids will have an ongoing role in a segment of the population. It should be determined what role 5-ASA should have in patients with CD in developing countries.

Treatment with azathioprine or 6-mercaptopurine (AZA/6-MP) is associated with remission rates of up to 60% (vs 21–35% for placebo)[19–23] (figure 2). In the respective trials, patients had usually had previous corticosteroid treatment. This suggests that, of the 30% of patients who will require immunosuppressive treatment, approximately half, or 15% overall, will not be sufficiently treated with purine analogues. Data from

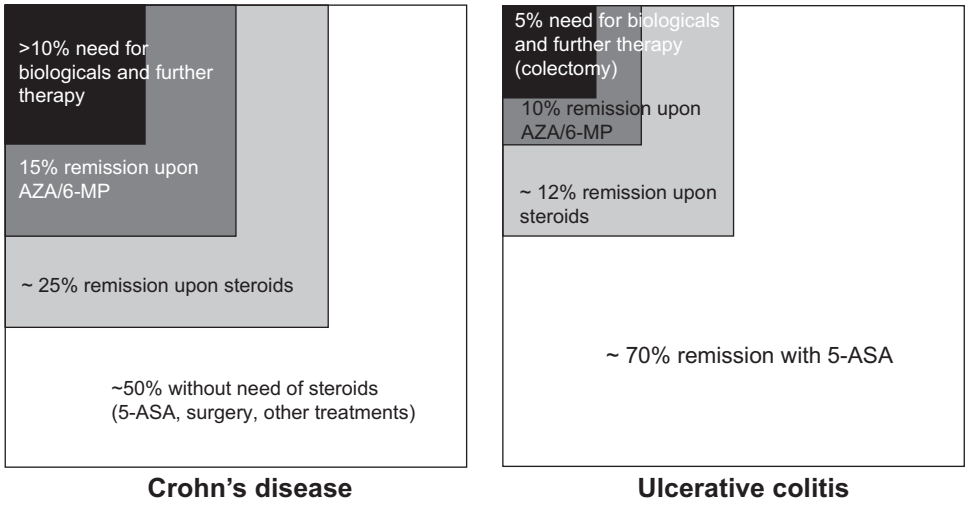

Figure 2 Efficacy of therapy in incidence cohorts and treatment studies of inflammatory bowel disease (IBD). Little more than 50% of patients with Crohn's disease (CD) require steroid treatment in incidence cohort studies. Steroid failure will leave approximately 40–50% of steroid-treated patients in need of other treatments such as azathioprine or 6-mercaptopurine (AZA/6-MP),[18] which achieve remission rates of up to 60%.[19–23] About 10–15% overall will not be sufficiently treated with purine analogues. In ulcerative colitis (UC), remission is achieved with 5-aminosalicylic acid (5-ASA) in around 50–70% of patients.[30–33] From a side effect perspective, 5-ASA is preferable to the cheaper sulfasalazine (<10% vs 30%). However, 5-ASA is not more effective than sulfasalazine. Corticosteroids are effective for induction of prolonged remission in ~50% of patients initially treated.[14] About 15–20% of patients with UC need more advanced therapy. AZA again will be effective for maintenance of remission in ~50% of the remaining patients, leaving ~ 5% requiring biological or alternative treatments such as colectomy.

the recent SONIC trial[23a] are less optimistic about the ability of thiopurines to effect a corticosteroid-free remission. A disadvantage of thiopurine therapy in developing countries is the need for regular blood count monitoring. Furthermore, immunosuppressive therapy poses an increased risk in countries with higher exposure to highly infectious diseases. Nevertheless, treatment can safely be maintained.[6] Methotrexate is a relatively inexpensive treatment that does not require such rigorous blood test monitoring; however, some monitoring of liver tests is required periodically.

Hence, there may be a 'therapeutic gap'[18] of 10–15% of patients with CD who cannot be sufficiently treated with therapies ranging from 5-ASA to corticosteroids to immunosuppressive therapy (figure 2). This is probably a minimum estimate, as there are other nuances to managing CD, such as the presence of fistulas that do not respond to antibiotics. Further, the data contributing to these estimates were exclusively derived from Western countries, and it remains to be determined whether CD in developing nations is phenotypically comparable to that in the West. Finally, just because it is inexpensive should not mean that people in developing nations should have to endure the ills of long-term corticosteroid therapy.

Should biological therapy fill the therapeutic void in the developing world? One-year remission rates of all patients initially treated with biological agents are at ~25%,[24–29] with a number needed to treat of four to five for most of the anti-TNF agents. Although much of the West practises an accelerated 'step-up' approach, it is unclear how early in the therapeutic armamentarium the developing world will be able to institute biological therapy.

UC TREATMENT NEEDS

5-ASA (mesalazine or mesalamine) is more effective for treatment of UC than treatment of CD. Response rates reported in randomised controlled trials of 5-ASA preparations in mild to moderately active UC peak at 84% at doses of 4.8 g[30–33] (figure 2). From a side effect perspective, 5-ASA is preferable to the cheaper sulfasalazine (<10% vs 30%). However, 5-ASA is not more effective than sulfasalazine. 5-ASA is also effective for the maintenance of remission (56–70%) compared with placebo (38%). Hence 50–65% of patients with UC will experience remission and maintain remission with 5-ASA, leaving <50% of patients needing intensified therapy. Corticosteroids are effective for acutely active UC.[34 35] In the Olmsted County cohort, 34% of patients with UC were treated with corticosteroids. Immediate outcomes for UC were complete remission in 54%, partial remission in 30%, and no response in 16%.[14] One-year outcomes for UC were prolonged response in 49%, corticosteroid dependence in 22%, and operation in 29%[14] (figure 2). This means that, of the 30–50% of patients with UC who are not effectively treated by 5-ASA, 50% may have a prolonged beneficial outcome after corticosteroid therapy, leaving about 15–20% needing more advanced therapy. Currently this remaining group of patients is typically treated with purine analogues and then stepped up to infliximab, and, in severe disease, they are treated with either ciclosporin/tacrolimus or infliximab. AZA may be effective for the induction and maintenance of remission in the population with corticosteroid-dependent UC.[36–39] Accounting for failure of remission maintenance with 5-ASA or purine analogues, then 5–10% of all patients will require more advanced therapy. Up to 82% of patients with severe UC refractory to other treatments responded to intravenous ciclosporin 4 mg/kg/day within 7 days versus 0% of patients receiving placebo.[40] While the toxicity of ciclosporin limits its appeal for the developing world, the need for frequent monitoring of drug level and serum biochemistry may also be a limitation. Anti-TNF therapy for UC can be beneficial, as the number needed to treat for a corticosteroid-free remission is four to five.[41] Certainly, colectomy is an option for patients with refractory UC (figure 2). Colectomy for UC may be associated with high initial costs, but over the long term it may be less expensive than long-term biological therapy. Trained surgeons are available in specialised centres such as in India, Malaysia, Mexico and Pakistan. However, access of these centres to patients is limited.

RECOMMENDATIONS OF THE WHO AND WORLD GASTROENTEROLOGY ORGANISATION (WGO)

Cost-effectiveness considerations are critical for the recommendations of the WGO for the treatment of IBD in developing countries, reflecting cost-effectiveness recommendations by the

WHO started in 1998. The WHO has published threshold values for intervention cost-effectiveness by region.[42] A drug or medical intervention is regarded as being 'very cost effective' if it costs <1 gross domestic product (GDP)/capita, 'cost effective' in a range between 1 and 3 GDP/capita, and not cost effective if it exceeds 3 GDP/capita. The GDP/capita was US$39 950 in North America, US$30 493 in Europe, US$10 208 in the Eastern Mediterranean region, US$4608 in South America, US$4959 in South East Asia, and US$1695 in Africa.[42 43] Subsequently the WHO has launched a 'CHOICE' project (CHOosing Interventions that are Cost-Effective) with the objective of 'providing policy makers with the evidence for deciding on the interventions and programmes which maximise health for the available resources'.[42] WHO-CHOICE reports the costs and effects of a wide range of health interventions in the 14 epidemiological sub-regions. The results of these cost-effectiveness analyses are collected in regional databases, which policy makers can adapt to their specific country setting.

It is very important to carefully adjust those cost-effectiveness models to country-specific conditions. They, for example, need to be modified to reflect the increased risk of infectious complications in specific regions. Given these risks, it is possible that overall quality-adjusted life years (QALYs) may not be higher for users of biological agents. Treatments regarded to be cost-effective in North America and Europe may not be cost-effective in developing countries, guiding resource consumption decision. Anti-TNF therapy has been determined to be effective, but the jury is still out as to whether it is cost-effective in the West.[44–46]

Owing to these considerations, the WGO recommends that, in countries with limited resources, sulfasalazine (as the cheapest treatment option) should be considered for all patients with mild to moderate Crohn's colitis and for maintenance of remission. Hydrocortisone enemas should initially be considered for distal colonic disease, and a trial of metronidazole considered for ileocolonic or colonic disease. Oral prednisone should be used for moderate to severe disease. If more resources are available, budesonide is recommended for mild ileal or ileocolonic disease (right colon). If patients fail to maintain remission after a course of corticosteroids, then AZA (or 6-MP) should be considered, and, in the case of AZA failure, methotrexate is recommended.

In the case of UC in a country with limited resources in endemic areas and limited access to diagnostics, a course of treatment for parasites should be given (and the nature of this therapy would depend on the endemic parasites such as *Entamoeba histolytica* or *Schistosoma mansonii*). In areas endemic for tuberculosis, a trial of anti-tuberculosis therapy for 1 month is recommended. Sulfasalazine is regarded as the therapy of choice for all mild to moderate colitis and for maintenance of remission according to these WGO suggestions. Different mesalazine preparations may be used as an alternative in cases of sulfasalazine intolerance. Hydrocortisone enemas should be used for distal colon disease. Oral prednisone is recommended for moderate to severe UC.

PRESENT PRACTICE OF BIOLOGICAL THERAPY ALLOCATION IN DEVELOPING COUNTRIES—SOME EXAMPLES

To set a basis for the necessary discussion, it is important to determine the major needs of patients with complicated IBD in developing countries. It appears that proper diagnosis and the high cost of biological therapy are the major problems.[7] There is an obvious gap between centres of population and rural areas.

In India, almost all leading hospitals have IBD centres. However, a major problem is a delayed diagnosis of CD, which may already cause disease complications such as strictures. The high cost of biological therapy is the main reason for the limited use of these drugs. There are an increasing number of patients with CD with complicated disease courses.[10] In India, infliximab is the only biological agent available. Fistulising disease is relatively rare, but still occurs. The requirement for biological therapy in India has been estimated to reach 10% for UC and 10–15% for CD. Regular maintenance therapy is rarely performed and a bridging strategy is usually applied.[10]

In Mexico, 10–15% of patients with IBD have a complicated or disabling disease course characterised by the need for surgery, more hospital admissions and corticosteroid dependence.[47–49] Only 10% are treated with anti-TNF agents because they have access to health insurance.[47–49] There are some specialist hospitals with the infrastructure to select patients for anti-TNF therapy and to establish the necessary surveillance strategies and even have a programme for the care of moderately to severely ill patients. Patients who lack health insurance have allocation problems in obtaining anti-TNF therapy. The Mexican government has recently initiated a programme of medical insurance named 'seguro popular' that provides drugs for the most common chronic diseases such as diabetes, hypertension, AIDS and cancer. However, IBD is not on the list.

In Malaysia, only the centre at the University of Malaya has a dedicated group of specialists focusing on IBD. There are few IBD specialised surgeons. Biological therapies are available but are not affordable.[2 50]

In Pakistan, UC is more common than CD and usually presents in the 3rd and 4th decade.[51] Men are more commonly affected than women. Many patients have a milder disease course. CD is now being increasingly recognised in Pakistan. In general, only a few patients are insured and have access to expensive biological therapies. The average cost of maintaining a patient on biological therapy is not bearable for a common Pakistani. The per capita income of Pakistan (2008) is US$1027, and the approximate cost of treatment is up to US$12000 (one million rupees) for eight doses in the first year.

These examples show that, in many countries of the developing world, there are dedicated centres able to provide state-of-the-art care for patients with IBD with complicated disease courses. The number of centres, however, differs from country to country. In general, disease courses are less severe; however, there are obviously patients who would benefit from anti-TNF therapy. Patient access to such therapy is limited by the high cost and the lack of a general insurance in such countries.

RISKS OF ANTI-TNF THERAPY IN DEVELOPING COUNTRIES

Beside the 'therapeutic need' suggested from the experience of doctors in the respective countries, other factors need to be considered.

Anti-TNFα agents can re-activate chronic viral hepatitis, with chronic hepatitis B being a major concern, since severe flares have been described.[52] This is a major issue in several Asian countries where hepatitis B (and hepatitis C) prevalence is high.[53–57] Active infections may be exacerbated, and quiescent infections may be activated during anti-TNFα therapy. Therefore patients should be screened for hepatitis B virus (HBV) infection before the start of treatment.[52] In patients with positive HBsAg and normal liver enzymes, prophylaxis should be considered, and regular monitoring of liver enzymes and HBV

DNA is recommended.[52] This may not always be possible in developing countries.

Diseases that require a host defence that is predominantly macrophage-dependent are of particular concern during anti-TNFα therapy. Tuberculosis is one of the three major global public health threats and causes substantial morbidity and mortality.[58] It is mandatory that active or latent tuberculosis be excluded before the start of anti-TNFα therapy. However, guidelines from developed countries may not fit in developing countries.[59] In countries with developed health systems, a tuberculin skin test (Mantoux test) is not considered to be the ideal screening test, as it can give false negative results in patients using corticosteroid or immunosuppressant therapy.[60–63] Therefore, in these countries, apart from the taking of a clinical history, both an in vitro test (T cell interferon-γ releasing assay (TIGRA)) and a chest x-ray are recommended. Since latent tuberculosis infections can affect the abdominal and mesenteric area, a chest x-ray on its own may not be sufficient. TIGRAs are minimally affected (Quantiferon-TB®Gold) or unaffected (T-Spot.TB®) by immunosuppressant therapy, but are expensive. The availability of TIGRA tests in developing countries is limited.[64 65] As the prevalence of tuberculosis in the general population in developing countries, especially the HIV-positive population in Africa, is still high,[66–69] this limits the potential use of TNFα antibodies in these countries.

For example, Mexico is considered to be an endemic area for tuberculosis infection. Intestinal tuberculosis constitutes the main differential diagnosis of CD, especially when disease is located in the terminal ileum or ileocaecal region. In addition to endoscopic characteristics, the diagnosis of intestinal tuberculosis is based on pathological findings as well as culture and PCR for *Mycobacterium tuberculosis* in the intestinal biopsy.

Guidelines and recommendations for screening and treatment have been published by international and national societies in developing countries, including PANLAR and the national societies in the Philippines, Hong Kong and India.[70 71] The Mantoux skin test has been found to be of limited value in India because of universal BCG vaccination at birth. Isonicotinylhydrazine (INH) prophylaxis for 9 months, or rifampicin for 4 months, is recommended in patients who require anti-TNF.[71] These guidelines contain both common recommendations and regional specificities according to regional epidemiology and experience.

Experience with anti-TNFα therapy has been reported from a number of Asian countries, such as India, South Korea, Philippines, Singapore and China.[72–76] Re-activation of tuberculosis has been observed in more than 10% of treated patients.[72] In a Korean study, over 2000 cases of tuberculosis per 100 000 person-years in infliximab-treated patients have been reported compared with 67 per 100 000 person-years in the general Korean population and 257 per 100 000 person-years in patients who had not received biological therapies.[73]

Besides tuberculosis, systemic fungal infections are a risk for patients treated with anti-TNFα therapy.[77–79] Fungal infections are common in circumstances of high humidity and reduced hygienic conditions. Another important factor that limits the use of anti-TNFα therapy in developing countries is the prevalence of HIV infections.[80 81] Uncontrolled HIV infection is a contraindication for the use of anti-TNFα therapy.

ETHICAL CONSIDERATIONS REGARDING THE USE OF BIOLOGICAL THERAPIES IN DEVELOPING COUNTRIES

Despite the potential obstacles to biological therapy in the developing world, these agents have an important role in managing IBD, and these therapies will have to be adapted for these countries. Specific protocols for the use of biological therapies need to be established in developing countries or in global regions, as defined by the WHO in its cost-effectiveness analyses. If anti-TNF therapy or other biological therapies are available for IBD, their use should be supervised by an experienced gastroenterologist. In Mexico, clinical guidelines for the use of anti-TNF agents have been developed for gastroenterologists in order to have a standard care of evaluation and rationale use of biological therapy.[82] Patients and their primary-care physicians need to be educated about the beneficial, and potential adverse, effects of these agents.

Very importantly, regular clinical supervision and laboratory assessments need to be performed for monitoring, as patients may have a subclinical or atypical presentation of an infection.[83] Once it is established how to use these agents in a specific jurisdiction (ie, is empiric antimicrobial therapy required up front? Can hepatitis B and HIV status be checked? Is regular blood monitoring available?), then a number of interested parties need to participate in enabling the provision of these drugs, including, but not limited to, the pharmaceutical industry, healthcare providers, patient advocate groups, governments and non-governmental organisations.

The question arises about how to place important, but expensive drugs with limited needs, unclear cost-effectiveness ratios and specific treatment risks that can even be fatal in the context of the developing world, with emerging healthcare organisations and limited resources.

While healthcare systems often try to solve the problem of scarcity by rationing, or increasing efficiency, ethics reflect the path of the just distribution of scarce goods. But how can such rationing be realised in a healthcare system? Non-medical criteria such as the patient's social function or age, although the subject of lively discussion, may be inappropriate. Simply considering the (small) number of patients who can be rescued may exclude access for patients who can really benefit from these agents. This raises the ethical dilemma that is considered in the West for many expensive cancer chemotherapies where either the cancers are rare or the benefits in terms of life expectancy are limited.

However, resources (and even very limited resources) belong to societies and therefore those societies expect a certain order in their allocation and utilisation. Resource allocation is the primary responsibility of any healthcare system. The high cost of medical treatment—specifically drugs such as anti-TNFα—which benefits only a few patients with IBD limits resources for other treatments, health promotion and disease prevention, all of which could benefit many people. In developing countries, medicine availability needs to be related to the social and community aspects of health and disease.

What alternative solutions could be considered to provide developing countries with anti-TNFα therapy for IBD patients who need them?

Perhaps programmes for the care of severely ill IBD patients in specialised national centres in developing countries that collaborate with IBD centres in industrialised countries could be initiated to help guide the use of biological therapy for IBD. This would guarantee an exchange of experience that may benefit both the developed and developing world.

We suggested that support needs to come from the manufacturers who will have reaped the rewards of their drug development programs in the west. In addition, we suggest starting a dialogue about experience with anti-TNF agents in the West and how it can be transferred most efficiently from countries with high availability to countries with so far very

limited availability. Experienced centres in certain developing countries will be able to allocate these drugs to the patients with IBD who need them. Although there is clearly less need in general and a greater number of risk factors associated with anti-TNF therapy in developing countries, these arguments are not sufficient to neglect the responsibility we have.

Funding MF discloses support by Astra Zeneca, Abbott, Merck, Nestle, Novartis, UCB. GR discloses grant support from Abbot, Ardeypharm, Essex, FALK, Flamentera, Novartis, Tillots, UCB and Zeller. CB has consulted for Abbot Canada, Astra Zeneca Canada and Janssen Canada, has received speaker's honoraria from Abbott Canada, Axcan Pharma and Shire Canada, has received an educational grant from Axcan Pharma, and has received a research grant from Abbott Canada.

Competing interests None.

Contributors GR wrote the manuscript, sent out questions for discussion, collected the statements from co-authors. CNB wrote the manuscript and contributed to the discussion. AS provided viewpoints, insights and information from India and contributed to the writing of the manuscript and the discussion. KLG provided viewpoints, insights and information from Malaysia and contributed to the writing of the manuscript and the discussion. JKY-F provided viewpoints, insights and information from Mexico and contributed to the writing of the manuscript and the discussion. ZA provided viewpoints, insights and information from Pakistan and contributed to the writing of the manuscript and the discussion. MF conceived the study, initiated the discussion, and contributed to the writing of the manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

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