see related editorial on page 225

CME

REVIEW

The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn's and Colitis Organization: Pregnancy and Pediatrics

Uma Mahadevan, MD[1], Salvatore Cucchiara, MD, PhD[2], Jeffrey S. Hyams, MD[3], Flavio Steinwurz, MD[4], F. Nuti[5], Simon P.L. Travis, MD[6], William J. Sandborn, MD[7] and Jean-Frederio Colombel, MD[8]

Women with inflammatory bowel disease (IBD) have similar rates of fertility to the general population, but have an increased rate of adverse pregnancy outcomes compared with the general population, which may be worsened by disease activity. Infertility is increased in those undergoing ileal pouch–anal anastomosis. Anti-tumor necrosis factor therapy in pregnancy is considered to be low risk and compatible with use during conception in men and women and during pregnancy in at least the first two trimesters. Infliximab (IFX) and certolizumab pegol are also compatible with breastfeeding, but safety data for adalimumab (ADA) are awaited. The safety of natalizumab during pregnancy is unknown. For children with Crohn's disease (CD), IFX is effective at inducing and maintaining remission. Episodic therapy is not as effective as scheduled infusions. Disease duration in children does not appear to affect the efficacy of IFX. IFX promotes growth in prepubertal and early pubertal Crohn's patients. It is also effective for the treatment of extraintestinal manifestations. ADA is effective for children with active CD and for maintaining remission, even if they have lost response to IFX, although there are fewer data. Vaccination of infants exposed to biological therapy *in utero* should be given at standard schedules during the first 6 months of life, except for live-virus vaccines such as rotavirus. Inactivated vaccines may be safely administered to children with IBD, even when immunocompromised.

Am J Gastroenterol 2011; 106:214–223; doi:10.1038/ajg.2010.464; published online 14 December 2010

INTRODUCTION

Many patients with inflammatory bowel disease (IBD) are of childbearing age. Advances in medical therapy have allowed more patients to enjoy symptomatic remission and as a result consider the option of parenthood. Determining the risk to benefit ratio for medical therapy during pregnancy and conception in patients with IBD is a complex equation, taking into account the desire of the parent to protect their child, the desire of the gastroenterologist to keep the parent healthy, and the desire of the obstetrician to avoid an adverse event during pregnancy. Into this mix one must add the scarcity of data on the safety of drugs during conception, pregnancy, and lactation, because pregnant women are not subjected to randomized trials for ethical reasons. Therefore, the treating physician must make their decision taking account of the views of the parent and the obstetrician, as well as the best available data. This paper presents the current evidence on efficacy and safety of biological therapy during pregnancy and when treating children. The process by which the evidence levels for this paper were derived are online (http://www.cebm.net/levels_of_evidence.asp#refs).

GENERAL CONSIDERATIONS OF BIOLOGICAL THERAPY DURING PREGNANCY AND BREAST FEEDING

World Congress of Gastroenterology (WCOG) Statement 3.1
Fertility, inflammatory bowel disease, and biological therapy

Women with inflammatory bowel disease have similar rates of fertility to the general population. Infertility is increased in those undergoing ileal pouch–anal anastomosis [EL 2a]

A systematic review reported an infertility rate of 12% before restorative proctocolectomy and 26% after surgery, based on seven studies and 945 evaluable patients (1). This represents a significant reduction in the ability to conceive after ileal pouch–anal anastomosis,

[1]Department of Gastroenterology, UCSF Center for Colitis and Crohn's Disease, San Francisco, California, USA; [2]Department of Pediatrics, University Hospital Umberto I, Sapienza University of Rome, Rome, Italy; [3]Department of Pediatric Gastroenterology, Connecticut Childrens Medical Center, Hartford, Connecticut, USA; [4]Department of Gastroenterology, Hospital Israelita Albert Einstein, São Paulo, Brazil; [5]Pediatric Gastroenterology and Liver Unit, Sapienza University, Rome, Italy; [6]Department of Gastroenterology, John Radcliffe Hospital, Oxford, UK; [7]Mayo Clinic, Rochester, Minnesota, USA; [8]Department of Hepato-Gastroenterology, Hospital Huriez, Lille, France. **Correspondence:** Uma Mahadevan, MD, Department of Medicine, University of California, 2330 Post Street no. 610, San Francisco, California 94115, USA. E-mail: uma.mahadevan@ucsf.edu
Received 1 March 2010; accepted 27 August 2010

although the impact is less than originally described (2,3). The reduction in fertility is thought to be the consequence of pelvic dissection involved in creating the pouch, leading to adhesions and tubal obstruction. The implications of pelvic surgery for fecundity are best discussed with women of childbearing age; the option of a subtotal colectomy with an ileostomy and later creation of a pouch after childbearing might be considered.

WCOG Statement 3.2
Effect of inflammatory bowel disease on the outcome of pregnancy

Women with inflammatory bowel disease have an increased rate of adverse pregnancy outcomes compared to the general population. While disease activity may itself increase the risk of adverse events, even women with inactive inflammatory bowel disease have higher rates of adverse events compared to the general population [EL 2b]

Early studies suggested that disease activity predicted an adverse outcome in pregnancy. Disease activity at conception has been associated with a higher rate of fetal loss and preterm birth (4,5) and disease activity during pregnancy associated with low birth weight and preterm birth (6,7). A more recent case–control study of hospitalized pregnant patients with IBD has also demonstrated an increase in preterm birth and low birth weight infants (8).

A community-based study from Northern California (Kaiser population), however, could not confirm that disease activity predicted an adverse outcome (9), even when limited to moderate or severe disease activity. Similarly, a population-based study from Denmark did not find an increased risk of adverse events associated with disease activity, except for an increase in the crude risk of preterm birth in those with moderate–high disease activity (odds ratio 3.4. 95% confidence interval 1.1–10.6) (10). Although population-based studies may not have enough patients to identify an adverse impact of severe disease, these two studies suggest that even without active disease, women with IBD have a higher risk of an adverse outcome of pregnancy. In any event, keeping the mother healthy and well nourished, off corticosteroids and out of the hospital is the goal of every pregnancy in a person with IBD. This often requires the continued use of biological therapy during conception and pregnancy.

Consequently, using infliximab (IFX or other biological therapy once an effect in ulcerative colitis (UC) is established) to avoid surgery for treatment-refractory UC is a valid therapeutic strategy, as it potentially preserves fertility in women of childbearing age. On the other hand, this necessitates continuing the medication throughout the years of conception and pregnancy.

THE USE OF SPECIFIC BIOLOGICAL THERAPIES DURING PREGNANCY AND BREAST FEEDING

In general, the greatest risk to mother and fetus during pregnancy is active IBD, and not the medication used to treat it. The Food and drug administration (FDA) has ascribed categories for drugs in pregnancy (**Table 1**), which are under review.

Table 1. Food and drug administration categories for drugs in pregnancy

A	Controlled studies show no risk
B	No evidence of risk in humans
C	Risk cannot be ruled out, animal studies revealed adverse effects on fetus
D	Positive evidence of risk in humans, risk/benefit ratio should be considered
X	Contraindicated

IFX in pregnancy

WCOG Statement 3.3
Effect of infliximab during pregnancy and breast feeding

Infliximab in pregnancy is considered to be low risk and compatible with use during conception in men and women and during pregnancy in at least the first two trimesters. It is also compatible with breastfeeding [EL 3b]

IFX, the FDA category B, is an IgG1 antibody, which is unlikely to cross the placenta in the first trimester, but very efficiently crosses the placenta in the late second and third trimester (11,12). Although this may protect the infant from exposure during the crucial period of organogenesis in the first trimester, crossing the placenta in the third trimester means that IFX can be present in the infant for several months from birth, raising concerns about infection and response to vaccines.

The two largest safety studies on IFX and pregnancy are from the TREAT Registry (13) and the Infliximab Safety Database (14) both maintained by Centocor (Malvern, PA, USA). Out of >6,200 patients enrolled by 2007, 168 pregnancies were reported, 117 of whom had previous IFX exposure. Fetal malformations occurred in two IFX-exposed pregnancies: ventricular septal defect and anencephaly. The rates of miscarriage (10 vs. 6.7%) and neonatal complications (6.9 vs. 10%) were not significantly different between IFX-treated and IFX-naïve patients, respectively.

The Infliximab Safety Database is a retrospective data-collection instrument. Pregnancy outcome data are available for 96 women with direct exposure to IFX (14). The data apply primarily to exposure during conception and the first trimester. The 96 pregnancies resulted in 100 births and expected vs. observed outcomes among women exposed to IFX were no different to those of the general population. A series of 10 women with intentional maintenance IFX use throughout pregnancy has also been reported (15). All 10 pregnancies ended in live births, with no reported congenital malformations. Another series reported 22 patients with exposure to IFX within 3 months of conception, continued until 20 weeks of gestation, at which time the drug was stopped to minimize placental transfer (16). Several of the patients had a flare of disease in the third trimester. There were three spontaneous abortions, one missed abortion, one stillbirth at 36 weeks (umbilical strangulation), two preterm births, three low birth weight infants, and no congenital anomalies.

A review of the FDA database (17) reported 61 anomalies in 41 children exposed to anti-tumor necrosis factor (TNF) agents *in utero*. Of these children, 24 out of 41 (59%) had one or more congenital anomalies that are part of the vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limp abnormalities (VACTERL) association. There were 34 specific types of congenital anomalies in total, and 19 (56%) of those were part of the VACTERL spectrum. This study has been criticized for the lack of denominator and the fact that there was only one complete VACTERL anomaly, whereas other defects were mostly cardiac in origin. Further study is clearly warranted and caution advisable.

Placental transfer of IFX is potentially important. A case report noted higher than maternal levels of IFX in an infant born to a mother receiving IFX throughout pregnancy, the last infusion being 2 weeks before delivery (18). The mother breast-fed and continued to receive IFX, but the infant's IFX concentration dropped over 6 months, suggesting placental rather than breast milk transfer. The duration of circulating IFX was longer in the neonate than in the mother. The effect of the high-IFX levels on the infant's developing immune system is not known, although at 7 months the infant had appropriate responses to vaccination. A case of fatal BCGitis has been reported in a child of a mother who was receiving IFX (below). In a case series of eight patients receiving IFX during pregnancy, all eight patients delivered healthy infants (19). In each case, the baby's serum IFX was higher than the mother's on the day of birth and it took anywhere from 2–7 months for the infant's IFX level to be undetectable. IFX was detected in cord blood in each case. This supports efficient placental transfer of IFX. The reason that IFX concentrations are higher and circulate for longer in infants is that their reticuloendothelial system is too immature to clear the antibody effectively, leading to slower clearance. Discontinuing IFX early in the third trimester or at the end of the second trimester may help to reduce IFX transport across the placenta and lower levels of serum IFX in the newborn. IFX can then be resumed immediately after delivery. If the mother flares during this time, it is our practice to give her the appropriate dose of IFX at the normally scheduled interval unless birth is imminent, though some argue management with corticosteroids should be considered for this short period.

IFX does not appear to cross via breast milk according to case reports (18,20,21) and will, in any case, not be absorbed after oral ingestion. In men, IFX has not been associated with congenital anomalies in a series of 10 patients (14). Semen quality appears unchanged, though a slight decrease in sperm motility and normal oval forms has been reported (22).

Adalimumab in pregnancy

WCOG Statement 3.4
Effect of adalimumab on pregnancy and breast feeding

Adalimumab in pregnancy is also considered low risk and compatible with use during conception and pregnancy in at least the first two trimesters [EL 4]. There are no safety data for breastfeeding or use in men attempting conception

Adalimumab (ADA), a pregnancy category B drug, is also an IgG1 antibody and should have similar placental transfer rates to IFX. There are case reports documenting the successful use of ADA to treat Crohn's disease (CD) during pregnancy, including one in which the patient received weekly dosing throughout pregnancy for a total of 38 doses (23,24). The Organization for Teratology Information Specialists reports 38 women enrolled in a prospective study of ADA in pregnancy and an additional 133 ADA-exposed pregnant women in a case-series (25). The rate of spontaneous abortion (5 out of 38, 13%) and stillbirth (0 out of 38) was similar to the disease-control and the general population taking into account reporting bias. The rates of congenital malformation (2 out of 33, 6.1%) and preterm delivery are also within the expected range in the non-disease controls.

Placental transfer of ADA, although probably similar to IFX, has not been confirmed, as levels cannot be checked commercially. Furthermore, because the drug is given every other week, it is more difficult to stop the drug early in the third trimester without risking a flare. In our practice, we consider stopping the agent 8–10 weeks before the estimated date of confinement. Once again because ADA concentrations cannot be checked commercially, the benefit or harm of this to the mother or fetus is unknown. There are no available data on breastfeeding or safety in men attempting conception while on ADA.

Certolizumab pegol in pregnancy

WCOG Statement 3.5
Effect of certolizumab pegol on the outcome of pregnancy and breast feeding

Certolizumab pegol in pregnancy is considered to be low risk and compatible with use during conception and pregnancy in women. It is also compatible with breastfeeding [EL 4]. There are no safety data for use in men attempting conception

Certolizumab pegol (CZP), the FDA category B, is a PEGylated Fab' fragment of a humanized anti-TNFα monoclonal antibody, so differs from IFX and ADA, which are IgG1 monoclonal antibodies. Fab' fragments cross the placenta by passive diffusion, unlike the active transfer of IgG1 antibodies, so the rates of transfer across the placenta in the third trimester are likely to be lower than IFX or ADA. Data from clinical trials report 16 patients who became pregnant while on CZP (data on file, UCB). A study of pregnant rats receiving a murinized IgG1 antibody of TNFα and a PEGylated Fab' fragment of this antibody, demonstrated much lower drug concentrations in the infant rat and breast milk with the Fab' fragment, compared with the full antibody (26). Data from four human births in patients who used CZP during pregnancy with the last dose 1–4 weeks before delivery found low levels of drug in the cord blood and in infant on the day of birth (27). Mothers' levels on the day of birth ranged from 4.9–59.6 μg/ml and infant levels varied from 0.4–1.0 μg/ml. In one patient, breast milk samples at various times did not have detectable levels of drug. A potential concern, however, is that the Fab' fragment may cross the placenta passively (albeit at low levels) during organogenesis in

the first trimester, though this may be true of all biological agents. Further human data are needed to determine the safety profile of this agent in pregnancy. There are no data on CZP and use in men during conception.

Natalizumab in pregnancy

WCOG Statement 3.6
Effect of natalizumab on the outcome of pregnancy and breast feeding

The safety of natalizumab during pregnancy is unknown. Although human data show no increased risk of birth defects, the agent is too new for adequate supportive data and there are no drugs of similar mechanism with which to compare it [EL 4]

Natalizumab (NAT) has the FDA pregnancy category C and is an IgG4 antibody. Like IgG1, IgG4 undergoes active transport across the placenta in the second and third trimester (11). There have been 164 pregnancies reported in patients with CD or multiple sclerosis who had received NAT during the first trimester (35 out of 164 had CD). There was no increase in the number of birth defects compared with that expected (28). Quite why NAT should receive the FDA category C, rather than the B for anti-TNF therapy is unclear, but appears to be due to the lack of a comparator with a similar mechanism and may have something to do with the exceptional occurrence of progressive multifocal leucoencephalopathy in adults. The individual needs of the patient should be judged against risk before using NAT during pregnancy.

There are data from eight men exposed to NAT at the time of conception, with no evidence of birth defects (28). There are no data on breastfeeding.

BIOLOGICAL THERAPY IN CHILDREN WITH CD

IFX in children

WCOG Statement 3.7
Effect of infliximab for children with Crohn's disease

Infliximab is effective at both inducing response and remission [EL 2b] and for maintaining response and remission in pediatric Crohn's disease [EL 2b]

There are no placebo-controlled, double-blind prospective studies of anti-TNF therapy, including IFX, in the treatment of CD in children. The largest study to date was the REACH trial (A Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF alpha Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate to Severe Crohn's Disease), which was a prospective, open-label investigation of three dose induction with IFX (5 mg/kg) in moderate to severely active pediatric CD, followed by doses at either 8- or 12-week intervals for maintenance (29). There have also been case series describing children receiving IFX in clinical practice (30–48).

The REACH study enrolled 112 patients (mean age 13.3 years, disease duration 2 years, 59% male) treated with 5 mg/kg at 0, 2, and 6 weeks (29). There was an 88% response and 59% were in remission at 10 weeks. At week 54, 33 out of 52 (64%) and 29 out of 52 (56%) patients receiving IFX every 8 weeks maintained a clinical response or remission, respectively, and had not required dose adjustment, compared with 17 out of 51 (33%) and 12 out of 51 (24%) receiving treatment every 12 weeks ($P = 0.002$ and $P < 0.001$, respectively). This demonstrates the superiority of 8-week over 12-week dosing for maintaining remission over 1 year. In a smaller open-label study, 83% of children receiving scheduled maintenance IFX infusions every 8 weeks were in remission at 1 year using the Harvey Bradshaw Index (HBI) as a marker of disease activity (49).

Two studies have examined follow-up for >1 year from initiation of IFX. One multicenter study involving 66 patients in the Netherlands (mean age at initiation of therapy 13.5 years) had a mean follow-up of 41 months (36). The authors estimated that 15% of patients had a prolonged response, 56% were IFX-dependent (requiring repeated infusions to maintain efficacy) and 29% lost response. A second multicenter study (50) examined 202 children (mean age 11.7 years) treated with 2,361 infusions (mean 12 per patient) with follow-up periods up to 3 years. In all, 128 of the study cohort had maintenance therapy with follow-up ≥1 year. Kaplan–Meier analysis showed the likelihood of continuing IFX was 93, 78, and 67% at 1, 2, and 3 years, respectively. In all, 49% required an increased dose or decreased interval. Clinical remission without the use of corticosteroids for the periods from 0–1, 1–2, and 2–3 years after starting IFX was 26, 44, and 33%, respectively.

WCOG Statement 3.8
Other effects of infliximab for children with Crohn's disease

Episodic therapy is not as effective as scheduled infusions for maintaining remission in pediatric Crohn's disease [EL 2b]. Infliximab is a corticosteroid sparing agent [EL 2b] and effective for achieving mucosal healing in pediatric Crohn's disease [EL 4]. Disease duration in children does not appear to affect the efficacy of infliximab [EL 4]

In a prospective, open-label study of the efficacy and safety of IFX as maintenance therapy for active pediatric CD comparing scheduled and "on demand" treatment strategies, 49 children were recruited (49). Their mean age was 13.9±2.2 years and they had a flare (HBI ≥5, and erythrocyte sedimentation rate (ESR) >20 mm/h) despite immunomodulators combined with steroids. Standard induction with IFX (5 mg/kg at 0, 2, and 6 weeks) was assessed at week 10 and responders were randomized to maintenance therapy over 1 year: group A, scheduled IFX every 2 months; group B, IFX on relapse. In all, 34 out of 40 children achieved remission during IFX induction therapy (HBI 6.7±2.5 at baseline vs. 1.1±1.5 at week 10, $P < 0.001$). After 1 year, 15 out of 18 (83%) on scheduled IFX were in remission (mean HBI 0.5), compared with 8 out of 13 (61%) children receiving IFX on demand ($P < 0.01$, mean HBI 3.2). The clinical relapse rate was 3 out of 13 (23%) in those on scheduled

therapy and 11 out of 12 (92%) in those receiving episodic therapy. Although the "delta" on the definition of remission was only 22%, the lack of symptoms (HBI 0.5) and low clinical relapse rate (23%) clearly confirms the superiority of scheduled therapy.

The REACH study (29) also demonstrated that corticosteroids could usually be tapered or discontinued in children with moderate to severe CD. Smaller studies have also shown the effectiveness of IFX for corticosteroid sparing (33,41,43–45). There are no controlled trials examining mucosal healing following IFX therapy in children with CD. A study of 18 children treated with three dose of induction with IFX demonstrated significantly improved endoscopic and histopathological activity at 8 weeks after initiation of therapy (32).

Data about whether a shorter duration of disease enhances the response to IFX in children are conflicting. Two studies (40,42) have suggested that early treatment (<2 years and <1 year, respectively, since diagnosis) was superior to treatment at a later date, but both studies included very small numbers of patients. In larger series of patients, there was no difference in outcome between patients treated at <1 year vs. >1 year (36) and <2 years vs. >2 years since diagnosis (51). This is in contrast to adults (see accompanying paper on When to Start biological therapy (52)).

ADA in children

WCOG Statement 3.9
Effect of adalimumab for children with Crohn's disease

Adalimumab is effective at inducing and maintaining remission in children with Crohn's disease [EL 3b]

There are limited data on the safety and efficacy of ADA for children with CD. A retrospective, single-center experience reported 15 subjects (median age 17.8 years, range 10–22 years, only 5 subjects <16 years of age) who had had either lost effect with IFX, or developed intolerance (53). Most patients were treated with ADA 80 mg initially and then 40 mg every other week. Of 14 patients with adequate follow-up, 7 were felt to have a complete response (cessation of corticosteroids or steroid-free interval >3 months) and 2 had a partial response (corticosteroid tapering). No serious side effects were reported. Another retrospective case series reviewed seven cases of CD previously treated with IFX, of whom five responded to ADA (54). Dosing schedules were variable and included both 40 and 80 mg initially, followed by 40 mg biweekly. The mean Pediatric Crohn's Disease Activity Index scores in patients before and after ADA were 12 and 4.2, respectively (remission ≤10). A prospective evaluation of 23 pediatric Crohn 's disease patients (9 naive and 14 intolerant or unresponsive to IFX) received ADA induction at weeks 0 and 2, and then every other week during a 48-week maintenance phase. At weeks 2, 4, 12, 24, and 48, remission rates were 36, 61, 31, 50, and 65%, respectively, whereas response rates were 87, 88, 70, 86, and 91%, respectively. No serious adverse events were reported (55).

A large multicenter experience with ADA involved 100 pediatric subjects from 12 sites. Almost all had previously been treated with IFX. A quarter had induction ADA with 160 mg at week 0 and 80 mg at week 2, half had 80 mg/40 mg and the remainder had other dosing schedules. Maintenance therapy was 40 mg every other week in 80% of subjects. Clinical response at 3, 6, and 12 months was 65, 71, and 70%, respectively, with steroid-free remission at 3, 6, and 12 months of 22, 33, and 42%, respectively (56).

CZP in children

There are no published studies of CZP in children; a trial of CZP in pediatric CD is currently underway.

NAT in children

WCOG Statement 3.10
Effect of natalizumab for children with Crohn's disease

Natalizumab is effective for inducing response and remission in children with Crohn's disease [EL 4]

There is a single study of NAT for CD in children (57). An open-label-dosing schedule of 3 mg/kg at weeks 0, 4, and 8 was administered to 31 adolescents with refractory CD. In all, 55% had a clinical response and 29% were in remission at 10 weeks. Mean α4-integrin saturation was 93% at 2 h and <40% at 4 weeks after the first and third infusions, suggesting that a higher dose might have been associated with improved efficacy.

BIOLOGICAL THERAPY IN CHILDREN WITH ULCERATIVE COLITIS

IFX for children with ulcerative colitis

WCOG Statement 3.11
Effect of biological therapy for children with ulcerative colitis

Infliximab is effective for induction and maintenance of remission in pediatric patients with moderate to severe ulcerative colitis unresponsive to conventional therapies [EL 3b]. Adalimumab is effective for patients who lose response or are intolerant of infliximab [EL 4]. There are no data on the use of certolizumab pegol for pediatric ulcerative colitis

Several series on children treated with IFX for severe UC unresponsive to conventional therapy are now available. A short-term clinical improvement in six out of nine pediatric patients at 2 weeks has been reported (58). The same group subsequently described a 2-year follow-up of these nine patients, plus an additional eight patients (59). Children received a variable number of infusions at varying intervals, but 63% still had a response at 2-year follow-up. A further retrospective series of 14 children with UC has reported a good response to IFX with newly diagnosed, steroid refractory acute severe colitis, or acute flare of long-standing colitis, but a poor response in steroid dependent colitis

(60). A follow-up report from the same authors (61), confirmed a better response in acutely ill patients, who could often discontinue immunomodulators and maintain remission after 1 year. In another 12 cases (62), IFX showed a good short-term response, but long-term response was low and one-third of the patients came to colectomy. A further retrospective study reported on 40 steroid-dependent or steroid-resistant children with ulcerative colitis. The response to IFX was 70%, with a significant delay or avoidance of surgery in the following 12 months (63). This is similar to results from an Italian study, showing remission in 55% of 22 children, followed (in responders) by a durable remission to week 54 (64). The largest cohort study recruited 332 pediatric patients with UC; 52 out of 332 received IFX and steroid-free inactive disease was observed in 38 and 21% of patients at 12 and 24 months, respectively. By 24 months, 61% of patients had avoided colectomy (65).

Consequently, IFX appears to be effective for children with moderate or severely active UC that is steroid-dependent or unresponsive to conventional treatment. An appreciable proportion of patients do not respond and up to one-third come to colectomy, so it is important to manage expectations (of parents and doctors, as much as the child). To this extent it is little different to adults (see the accompanying paper on Safety (66)). Large multicenter controlled trials are needed to define the usefulness of IFX in different subgroups, maintenance strategies and long-term safety profile in the pediatric population.

Other biological therapy for children with ulcerative colitis

A case series reported the use of ADA in three pediatric patients with UC who had lost response or were intolerant of IFX (67). Two of three patients responded, with the non-responder requiring colectomy. There are no published data on the use of CZP for pediatric ulcerative colitis.

BIOLOGICAL THERAPY FOR EXTRAINTESTINAL MANIFESTATIONS OF IBD IN CHILDREN

WCOG Statement 3.12
Effect of anti-TNF therapy for extraintestinal manifestations in children

Infliximab promotes growth improvement in prepubertal and early-pubertal Crohn's patients [EL 2b]. It is also effective for the treatment of cutaneous extraintestinal manifestations and uveitis. [EL 3b]

Adalimumab is effective for the treatment of uveitis in pediatric Crohn's disease [EL 3b]

Growth failure and pubertal delay are specific to the management of children and adolescents with CD and may challenge their quality of life. The final adult height is known to be a determinant of an individual's success in life, whereas short stature in adolescence has an impact on psychological and emotional well-being and development (68,69). This affects the goals for managing pediatric CD, which are symptomatic, steroid-free remission, with mucosal healing and enhancement of growth and pubertal development.

The etiology of growth failure is multifactorial and still poorly understood. Disease-related factors, such as malnutrition, the inflammatory process (with proinflammatory cytokines being directly implicated), and steroid therapy appear to be the main determinants (70). Achieving a sustained, steroid-free remission therefore becomes a priority in childhood, until growth is completed (71).

Cytokines, including TNF α, have a pivotal role in growth retardation, so more attention has focused on biological therapies. IFX has been reported to be effective in small cohorts for improvement of height *Z*-scores over time in children with severe CD, unresponsive to conventional drugs (32,33,72).

More recently, the REACH study has shown that IFX maintenance therapy improves growth and pubertal development, which emphasizes the importance of maintaining remission (29). The best results were obtained in children treated either before the onset of puberty or in its early stages (Tanner I–III). This has been confirmed in a further randomized open-label trial of IFX, comparing scheduled to on demand maintenance therapy. Better growth and development occurred in the scheduled infusion group (49). Nevertheless, discouraging data have been reported from a prospective multicenter study on newly diagnosed children with CD (73). If growth abnormalities were present at diagnosis, then these persisted during the first 2 years of treatment, despite treatment paradigms that included IFX, which appeared only to improve growth, but not at a statistically significant rate.

As for other extraintestinal manifestations, IFX appears to work well in those that have a link to active CD. Case reports have noted that IFX is effective for pediatric patients with pyoderma gangrenosum, orofacial involvement, erythema nodosum, or idiopathic lymphedema (74,75). IFX (76–78) and ADA (79,80) have both proved effective for pediatric patients with uveitis in small prospective studies.

COMPLICATIONS OF BIOLOGICAL THERAPY IN CHILDREN

WCOG Statement 3.13
Risks of biological therapy in children

Biological agents are effective, yet carry a small, but significantly increased risk of infection. They should therefore be used with caution in children [EL 4]. Hepatosplenic T-cell lymphoma has been reported in patients on infliximab or adalimumab used in combination with azathioprine or mercaptopurine [EL 4]

Infection

Screening for and treatment of latent tuberculosis before initiating anti-TNF therapy reduces the risk of developing active infection (81,82). Immunomodulators, especially when used in combination, are associated with an increased risk of opportunistic infections, such as herpes zoster, histoplasmosis, or listeria (83) (see the accompanying paper on "Safety"(66)). Children treated with

combinations of immunomodulators should receive careful monitoring for infectious complications. No evidence-based advice can be given about the monitoring frequency, but planned checks on the complete blood count and ready access to telephone advice or the clinic are generally considered essential.

Parasitic infection can be serious and become systemic in patients on immunomodulators. The need to screen varies with the geographical location, prevalence of infection, diagnostic sensitivity, and likely benefit (84). It has to be accepted that although the safety profile of anti-TNF therapy in clinical trials is good, the risk of opportunistic infection is increased, especially in patients on anti-TNF therapy combined with immunomodulators or corticosteroids.

Hepatosplenic T-cell lymphoma

Therapeutic strategies to control inflammation in IBD best involve combinations of treatment, but more aggressive the treatment strategy, the greater the safety concern. Azathioprine and mercaptopurine are associated with an increased risk of non-Hodgkin's lymphoma (85). B-cell lymphoma has also been associated with anti-TNF therapy (86). An aggressive, frequently fatal form of lymphoma, hepatosplenic T-cell lymphoma (87,88), has been reported in adolescents and young adults, but now also in older patients, treated with anti-TNF therapy. To date, about 20 cases have been reported, all on anti-TNF with thiopurine therapy (see accompanying paper (66)). Most have been associated with IFX, but at least two cases have been associated with IFX followed by ADA. Before the advent of biological therapy, hepatosplenic T-cell lymphoma had been reported in patients with IBD receiving thiopurines alone (89). As the number of subjects treated with biological therapy relative to the number of hepatosplenic T-cell lymphoma is not known, the presence of any association is speculative. Given the lack of objective data, it is not possible to give definitive advice: the risks and benefits of dual therapy compared with monotherapy have to be evaluated separately, for each patient (90).

Infusion reactions

WCOG Statement 3.14
Infusion reactions in children

Induction with three doses of infliximab, administered at 0, 2, and 6 weeks, followed by scheduled doses every 8 weeks increases efficacy and safety. Premedication is not routinely needed. Adalimumab is effective for children with active Crohn's disease and for maintaining remission, even if they have lost response to infliximab [EL 3b]

Antibody formation against IFX is more pronounced in those patients receiving episodic therapy and diminishes the effect of IFX (33,41,45,91–94). Premedication with hydrocortisone does not prevent the development of infusion reactions in children, but once an infusion reaction has occurred, premedication may be indicated to prevent subsequent infusion reactions (91–93,95) Concomitant immunomodulators may reduce the risk of IFX antibody formation and infusion reactions (45,94), but the association is complex (see accompanying paper (52)).

ADA is a safe and effective substitute for children who become intolerant of IFX (53,56). The rate of infusion reactions in children receiving IFX is similar to that in adults (41,45). IFX is well tolerated in children with CD. Anaphylactic reactions are rare. In a total of 88 patients receiving 450 infusions, 13 developed mild infusion reactions, 5 during the initial infusion. All infusion reactions were limited, but required reduction in the flow rate and the use of prednisolone plus chlorpheniramine and acetaminophen (paracetamol) (41). Female gender, immunomodulators for <4 months and previous infusion reactions may be risk factors for subsequent infusion reactions in children. Pretreatment with hydrocortisone at the time of the IFX infusion reduces antibody formation (95), although the association between antibody formation, infusion reaction, and response is remarkably opaque (52).

In a pediatric cohort of patients with CD ($n=28$) treated with IFX, sensitization occurred in 36% patients, which was in turn associated with a loss of response to maintenance infusions (96). Severe infusion reactions occurred in (only) two patients with high titers of antibody to IFX. Serum concentrations of IFX were reduced by the presence of anti-IFX antibodies. Although the authors suggest that measuring circulating antibodies to IFX represents an indirect, but reliable method of monitoring therapy, measurement of drug concentrations would be a more direct approach. The complex nature of response involves more than drug (let alone antibody) concentration alone (97).

VACCINATION OF INFANTS AND CHILDREN EXPOSED TO BIOLOGICAL THERAPY

WCOG Statement 3.15
Vaccinations in infants exposed to biological therapy *in utero*

Vaccination of infants exposed to biological therapy *in utero* should be given at standard schedules, except for live-virus vaccines, which are best not given if circulating biological agents are detectable in the infant [EL 5]

Live virus vaccines are contraindicated for patients receiving biological therapy. Live virus vaccines that may be given in the first 6 months of life include rotavirus, intranasal influenza vaccine, and Bacillus Calmette–Guérin (BCG). Vaccination with live virus agents should be deferred in infants exposed *in utero* to IFX or ADA, unless serum levels are undetectable. CZP concentrations should be undetectable by the time of rotavirus vaccination. A case report notes death from disseminated BCG in an infant vaccinated at 3 months of age. The infant's mother received IFX for CD throughout pregnancy (98).

WCOG Statement 3.16
Vaccinations in children receiving biological therapy

Inactivated vaccines may be safely administered to children with inflammatory bowel disease, even when immunocompromised [EL 3b]. The use of live-virus vaccines in pediatric patients receiving biological therapy is contraindicated [EL 5]

Inactivated influenza vaccine is best given yearly to immunosuppressed children of 6 months of age and older, before each influenza season (99,100). Inactivated polio vaccine is indicated, as well as diphtheria–tetanus–pertussis, *Haemophilus influenzae* b conjugate vaccine, hepatitis A and B, and meningococcal vaccination (101,102).

The ability to develop an adequate immunological response appears to depend on the presence of immunosuppression *during* or *within* 2 weeks of immunization in children with secondary immunodeficiency (e.g., secondary to medication). The immune response to inactivated vaccines (hepatitis A and B, meningococcal, and influenza) (99–103) may be attenuated in these circumstances. On the other hand, an adequate immune response occurs between 3 months and 1 year after discontinuation of immunosuppressive therapy (104). In pediatric patients with IBD who are not on immunomodulators, a serological conversion rate to influenza vaccine of 33–85% has been reported. Patients on concomitant IFX and immunomodulatory therapy are at higher risk of an inadequate response to vaccination. Serological testing to confirm a response is best considered if there is concern. The influenza vaccine was safe and did not affect disease activity (58,99).

Reactivation of hepatitis B after IFX administration, however, has been reported, which is why vaccination is recommended in case the child needs treatment with biological therapy (103). The reason for recommending vaccination against human papilloma virus to young females (national recommendations for age limits vary) is because there appears to be an increased risk of cervical dysplasia on immunosuppression (104).

CONCLUSIONS

Biological agents are a very effective and low risk therapy for pregnant women and children with IBD. However, special accommodation must be considered for the timing of dosing in pregnant women and vaccinations in their offspring. Among children with IBD, the benefits with respect to disease remission, steroid sparing, growth, and development seem to outweigh the small, but significant risk of complications. In both populations, more data are needed, particularly with respect to the newer biological formulations.

ACKNOWLEDGMENTS

We are grateful to Nicole Eichinger and Sonja Rosensweig, secretariat of the European Crohn's and Colitis Organisation, for their help with the logistics of the meetings and to Christine Mazziotta for technical assistance in preparing the manuscripts.

CONFLICT OF INTEREST

Guarantor of the article: Uma Mahadevan, MD.

Specific author contributions: Uma Mahadevan wrote pregnancy section and edited the entire paper; Cucchiara S. and Nuti F. wrote the sections on IFX/UC and IFX and growth in CD; Hyams J. wrote section on biologics and pediatric CD; Steinwurz F. wrote section on pediatric immunogenicity, infection, extra-intestinal manisfestation, and vaccination; Travis S.P.L., Sandborn W.J., and Colombel J.F. are the overall editors of all the WCOG statement papers. Also served as the final consensus panel for the level of evidence.

Financial support: None.

Potential competing interests: None. However, several of the authors serve as consultants for Centocor, Abbott, UCB, and Elan and/or have received research support from these companies.

REVIEW

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Biological therapy for Crohn's disease has proven effective in randomized controlled trials, but pregnant and breastfeeding women have been excluded from these trials.
- ✓ Fewer and smaller studies of biologics in children (vs. adults) have been published.
- ✓ Although biological efficacy is proven in women and children, questions remain about the use of biologics in pregnancy and in children.

WHAT IS NEW HERE

- ✓ These World Congress of Gastroenterology consensus statements summarize the available data on biological efficacy and safety in pregnancy and breastfeeding, and in children.
- ✓ Inactivated vaccines on standard schedules are recommended for children exposed to biological therapy *in utero*, but live-virus vaccines should be delayed until after biological molecules are no longer likely to be circulating in the child's blood, which can require several months.

REFERENCES

1. Waljee A, Waljee J, Morris AM *et al.* Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. Gut 2006;55:1575–80.
2. Lepisto A, Sarna S, Tiitinen A *et al.* Female fertility and childbirth after ileal pouch-anal anastomosis for ulcerative colitis. Br J Surg 2007;94:478–82.
3. Olsen KO, Juul S, Berndtssoni I *et al.* Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. Gastroenterology 2002;122:15–9.
4. Morales M, Berney T, Jenny A *et al.* Crohn's disease as a risk factor for the outcome of pregnancy. Hepatogastroenterology 2000;47:1595–8.
5. Nielsen OH, Andreasson B, Bondesen S *et al.* Pregnancy in ulcerative colitis. Scand J Gastroenterol 1983;18:735–42.
6. Bush MC, Patel S, Lapinski RH *et al.* Perinatal outcomes in inflammatory bowel disease. J Matern Fetal Neonatal Med 2004;15:237–41.
7. Fedorkow DM, Persaud D, Nimrod CA *et al.* Inflammatory bowel disease: a controlled study of late pregnancy outcome. Am J Obstet Gynecol 1989;160:998–1001.
8. Reddy D, Murphy SJ, Kane SV *et al.* Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. Am J Gastroenterol 2008;103:1203–9.
9. Mahadevan U, Sandborn WJ, Li DK *et al.* Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterology 2007;133:1106–12.
10. Norgard B, Hundborg HH, Jacobsen BA *et al.* Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional danish cohort study. Am J Gastroenterol 2007;102:1947–54.
11. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol 2009;104:228–33.
12. Simister NE. Placental transport of immunoglobulin G. Vaccine 2003;21:3365–9.
13. Lichtenstein GR, Feagan BG, Cohen RD. *et al.* Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621–30.

14. Katz JA, Antoni C, Keenan GF *et al.* Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol 2004;99:2385–92.
15. Mahadevan U, Kane S, Sandborn WJ *et al.* Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. Aliment Pharmacol Ther 2005;21:733–8.
16. Schnitzler F, Fickler HH, Ferrante M *et al.* Intentional treatment with infliximab during pregnancy in women with inflammatory bowel disease. Gastroenterology 2007;132:A144.
17. Carter JD, Ladhani A, Ricca LR *et al.* A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. J Rheumatol 2009;36:635–41.
18. Vasiliauskas EA, Church JA, Silverman N *et al.* Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. Clin Gastroenterol Hepatol 2006;4:1255–8.
19. Mahadevan U, Terdiman JP, Church J *et al.* Infliximab levels in infants born to women with inflammatory bowel disease. Gastroenterology 2007;132:A144.
20. Kane S, Ford J, Cohen R *et al.* Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. J Clin Gastroenterol 2009;43:613–6.
21. Peltier M, James D, Ford J *et al.* Infliximab levels in breast-milk of a nursing Crohn's patient. Am J Gastroenterol 2001;96:P258.
22. Mahadevan U, Terdiman JP, Aron J *et al.* Infliximab and semen quality in men with inflammatory bowel disease. Inflamm Bowel Dis 2005;11:395–9.
23. Coburn LA, Schwartz DA. The successful use of adalimumab to treat active Crohn's disease of an ileoanal pouch during pregnancy. Am J Gastroenterol 2005;100:S176.
24. Mishkin DS, Van Deinse W, Becker JM *et al.* Successful use of adalimumab (Humira) for Crohn's disease in pregnancy [3]. Inflamm Bowel Dis 2006;12:827–8.
25. Johnson DL, Jones KL, Chambers CD *et al.* Pregnancy outcomes in women exposed to adalimumab: the OTIS autoimmune diseases in pregnancy project. Gastroenterology 2009;136:A–27.
26. Nesbitt A, Foulkes R. Placental transfer and accumulation in milk of the anti-TNF antibody TN3 in rats: immunoglobulin G1 versus PEGylated Fab. Am J Gastroenterol 2006;106:S119.
27. Mahadevan U. Certolizumab use in pregnancy: low levels detected in cord blood. Gastroenterology 2009;136:A960.
28. Nazareth M, Cristiano L, Kooijmans M *et al.* Natalizumab use during pregnancy. Am J Gastroenterol 2008;104:S114.
29. Hyams J, Crandall W, Kugathasan S *et al.* Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007;132:863–73.
30. Afzal NA, Ozzard A, Keady S *et al.* Infliximab delays but does not avoid the need for surgery in treatment-resistant paediatric Crohn' disease. Dig Dis Sci 2007;52:3329–33.
31. Baldassano R, Braegger CP, Escher JC *et al.* Infliximab (REMICADE) therapy in the treatment of paediatric Crohn's disease. Am J Gastroenterol 2003;98:833–8.
32. Borrelli O, Bascietto C, Viola F *et al.* Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. Dig Liver Dis 2004;36:342–7.
33. Cezard JP, Nouaili N, Talbotec C *et al.* A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (remicade) in severe paediatric crohn disease. J Pediatr Gastroenterol Nutr 2003;36:632–6.
34. De Ridder L, Benninga MA, Taminiau JA *et al.* Infliximab as first-line therapy in severe paediatric Crohn's disease. J Pediatr Gastroenterol Nutr 2006;43:388–90.
35. De Ridder L, Escher JC, Bouquet J *et al.* Infliximab therapy in 30 patients with refractory paediatric crohn disease with and without fistulas in The Netherlands. J Pediatr Gastroenterol Nutr 2004;39:46–52.
36. De Ridder L, Rings EH, Damen GM *et al.* Infliximab dependency in paediatric Crohn's disease: long-term follow-up of an unselected cohort. Inflamm Bowel Dis 2008;14:353–8.
37. Hyams JS, Markowitz J, Wyllie R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. J Pediatr 2000;137:192–6.
38. Kooros K, Katz AJ. Infliximab therapy in paediatric Crohn's pouchitis. Inflamm Bowel Dis 2004;10:417–20.
39. Kugathasan S. Prolonged duration of response to infliximab in early paediatric Crohn's disease. J Pediatr Gastroenterol Nutr 2001;33 (Suppl 1): S40–3.
40. Kugathasan S, Werlin SL, Martinez A *et al.* Prolonged duration of response to infliximab in early but not late paediatric Crohn's disease. Am J Gastroenterol 2000;95:3189–94.
41. Lamireau T, Cezard JP, Dabadie A *et al.* Efficacy and tolerance of infliximab in children and adolescents with Crohn's disease. Inflamm Bowel Dis 2004;10:745–50.
42. Lionetti P, Bronzini F, Salvestrini C *et al.* Response to infliximab is related to disease duration in paediatric Crohn's disease. Aliment Pharmacol Ther 2003;18:425–31.
43. Markowitz J, Hyams J, Mack D *et al.* Corticosteroid therapy in the age of infliximab: acute and 1-year outcomes in newly diagnosed children with Crohn's disease. Clin Gastroenterol Hepatol 2006;4:1124–9.
44. Serrano MS, Schmidt-Sommerfeld E, Kilbaugh TJ *et al.* Use of infliximab in paediatric patients with inflammatory bowel disease. Ann Pharmacother 2001;35:823–8.
45. Stephens MC, Shepanski MA, Mamula P *et al.* Safety and steroid-sparing experience using infliximab for Crohn's disease at a paediatric inflammatory bowel disease center. Am J Gastroenterol 2003;98:104–11.
46. Teitelbaum JE, Saeed S, Triantafyllopoulou M *et al.* Infliximab in paediatric Crohn disease patients with enterovesicular fistulas. J Pediatr Gastroenterol Nutr 2007;44:279–82.
47. Wewer V, Riis L, Vind I *et al.* Infliximab dependency in a national cohort of children with Crohn's disease. J Pediatr Gastroenterol Nutr 2006;42:40–5.
48. Wynands J, Belbouab R, Candon S *et al.* 12-Month follow-up after successful infliximab therapy in paediatric crohn disease. J Pediatr Gastroenterol Nutr 2008;46:293–8.
49. Ruemmele FM, Lachaux A, Cezard JP *et al.* Efficacy of infliximab in paediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflamm Bowel Dis 2009;15:388–94.
50. Hyams JS, Lerer T, Griffiths A *et al.* Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. Inflamm Bowel Dis 2009;15:816–22.
51. Hyams J, Crandall W, Kugathasan S *et al.* Disease duration does not affect outcome following infliximab in children with Crohn's disease. Am J Gastroenterol 2008;103:S533.
52. D'Haens G, Panaccione R, Higgins PDR *et al.* The London Position Statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organisation: When to start, when to stop, which drug to choose and how to predict response? Am J Gastroenterol 2010; 2 November 2010 (e-pub ahead of print).
53. Wyneski MJ, Green A, Kay M *et al.* Safety and efficacy of adalimumab in paediatric patients with Crohn disease. J Pediatr Gastroenterol Nutr 2008;47:19–25.
54. Noe JD, Pfefferkorn M. Short-term response to adalimumab in childhood inflammatory bowel disease. Inflamm Bowel Dis 2008;14:1683–7.
55. Viola F, Civitelli F, Di Nardo G *et al.* Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. Am J Gastroenterol 2009;104:2566–71.
56. Rosh J, Lerer T, Markowitz J *et al.* Retrospective evaluation of the safety and effect of adalimumab therapy (RESEAT) in Paediatric Crohn's Disease. Am J Gastroenterol 2009;104:3042–9.
57. Hyams JS, Wilson DC, Thomas A *et al.* Natalizumab therapy for moderate to severe Crohn disease in adolescents. J Pediatr Gastroenterol Nutr 2007;44:185–91.
58. Mamula P, Markowitz JE, Brown KA *et al.* Infliximab as a novel therapy for paediatric ulcerative colitis. J Pediatr Gastroenterol Nutr 2002;34:307–11.
59. Mamula P, Markowitz JE, Cohen LJ *et al.* Infliximab in paediatric ulcerative colitis: two-year follow-up. J Pediatr Gastroenterol Nutr 2004;38:298–301.
60. Russell GH, Katz AJ. Infliximab is effective in acute but not chronic childhood ulcerative colitis. J Pediatr Gastroenterol Nutr 2004;39:166–70.
61. Fanjiang G, Russell GH, Katz AJ. Short- and long-term response to and weaning from infliximab therapy in paediatric ulcerative colitis. J Pediatr Gastroenterol Nutr 2007;44:312–7.
62. Eidelwein AP, Cuffari C, Abadom V *et al.* Infliximab efficacy in paediatric ulcerative colitis. Inflamm Bowel Dis 2005;11:213–8.
63. McGinnis JK, Murray KF. Infliximab for ulcerative colitis in children and adolescents. J Clin Gastroenterol 2008;42:875–9.
64. Cucchiara S, Romeo E, Viola F *et al.* Infliximab for paediatric ulcerative colitis: a retrospective Italian multicenter study. Dig Liver Dis 2008;40 (Suppl 2): S260–4.
65. Hyams JS, Lerer T, Griffiths A *et al.* Outcome following infliximab therapy in children with ulcerative colitis. Am J Gastroenterol 2010;105:1430–6.
66. Van Assche G, Lewis JD, Lichtenstein G *et al.* The London Position Statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organisation: Safety. Am J Gastroenterol 2011 (in press).

67. Noe J, Pfefferkorn M. Short-term response to adalimumab in childhood inflammatory bowel disease. Inflamm Bowel Dis 2008;14:1683–7.
68. Hensley WE, Cooper R. Height and occupational success: a review and critique. Psychol Rep 1987;60:843–9.
69. Molinari E, Sartori A, Ceccarelli A *et al.* Psychological and emotional development, intellectual capabilities, and body image in short normal children. J Endocrinol Invest 2002;25:321–8.
70. Shamir R, Phillip M, Levine A. Growth retardation in paediatric Crohn's disease: pathogenesis and interventions. Inflamm Bowel Dis 2007;13: 620–8.
71. Cochrane DSR. Interventions for growth failure in childhood Crohn's disease. Cochrane Database 2005;20:CD003873.
72. Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. Inflamm Bowel Dis 2007;13:424–30.
73. Pfefferkorn M, Burke G, Griffiths A *et al.* Growth abnormalities persist in newly diagnosed children with crohn disease despite current treatment paradigms. J Pediatr Gastroenterol Nutr 2009;48:168–74.
74. Batres LA, Mamula P, Baldassano RN. Resolution of severe peristomal pyoderma gangrenosum with infliximab in a child with Crohn disease. J Pediatr Gastroenterol Nutr 2002;34:558–60.
75. Kugathasan S, Miranda A, Nocton J *et al.* Dermatologic manifestations of Crohn disease in children: response to infliximab. J Pediatr Gastroenterol Nutr 2003;37:150–4.
76. Rajaraman RT, Kimura Y, Li S *et al.* Retrospective case review of paediatric patients with uveitis treated with infliximab. Ophthalmology 2006;113: 308–14.
77. Richards JC, Tay-Kearney ML, Murray K *et al.* Infliximab for juvenile idiopathic arthritis-associated uveitis. Clin Experiment Ophthalmol 2005;33:461–8.
78. Suhler EB, Smith JR, Wertheim MS *et al.* A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol 2005;123:903–12.
79. Biester S, Deuter C, Michels H *et al.* Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol 2007;91:319–24.
80. Vazquez-Cobian LB, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. J Pediatr 2006;149:572–5.
81. Gupta A, Street AC, Macrae FA. Tumour necrosis factor alpha inhibitors: screening for tuberculosis infection in inflammatory bowel disease. Med J Aust 2008;188:168–70.
82. Irving PM, Gibson PR. Infections and IBD. Nat Clin Pract Gastroenterol Hepatol 2008;5:18–27.
83. Toruner M, Loftus EV Jr, Harmsen WS *et al.* Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008;134:929–36.
84. Rahier J-F, Ben-Horin S, Eser A *et al.* European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's and Colitis 2009;3:47–91.
85. Kandiel A, Fraser AG, Korelitz BI *et al.* Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut 2005;54:1121–5.
86. Siegel CA, Hur C, Korzenik JR *et al.* Risks and benefits of infliximab for the treatment of Crohn's disease. Clin Gastroenterol Hepatol 2006;4: 1017–24.
87. Mackey AC, Green L, Leptak C *et al.* Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease: update. J Pediatr Gastroenterol Nutr 2009;48:386–8.
88. Mackey AC, Green L, Liang LC *et al.* Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2007;44:265–7.
89. Rosh JR, Gross T, Mamula P *et al.* Hepatosplenic T-cell lymphoma in adolescents and young adults with Crohn's disease: a cautionary tale? Inflamm Bowel Dis 2007;13:1024–30.
90. Cucchiara S, Escher JC, Hildebrand H *et al.* Paediatric inflammatory bowel diseases and the risk of lymphoma: should we revise our treatment strategies? J Pediatr Gastroenterol Nutr 2009;48:257–67.
91. Crandall WV, Mackner LM. Infusion reactions to infliximab in children and adolescents: frequency, outcome and a predictive model. Aliment Pharmacol Ther 2003;17:75–84.
92. Diamanti A, Castro M, Papadatou B *et al.* Severe anaphylactic reaction to infliximab in paediatric patients with Crohn's disease. J Pediatr 2002;140:636–7, author reply 637.
93. Jacobstein DA, Markowitz JE, Kirschner BS *et al.* Premedication and infusion reactions with infliximab: results from a paediatric inflammatory bowel disease consortium. Inflamm Bowel Dis 2005;11:442–6.
94. Veres G, Baldassano RN, Mamula P. Infliximab therapy in children and adolescents with inflammatory bowel disease. Drugs 2007;67:1703–23.
95. Puchner TC, Kugathasan S, Kelly KJ *et al.* Successful desensitization and therapeutic use of infliximab in adult and paediatric Crohn's disease patients with prior anaphylactic reaction. Inflamm Bowel Dis 2001;7:34–7.
96. Candon S, Mosca A, Ruemmele F *et al.* Clinical and biological consequences of immunization to infliximab in paediatric Crohn's disease. Clin Immunol (Orlando) 2006;118:11–9.
97. Cassinnotti A, Travis SPL. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. Inflamm Bowel Dis 2009;15:1264–75.
98. Cheent K, Nolan J, Shariq S *et al.* Case Report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's Disease. J Crohn's Colitis 2010, 4:603–5.
99. Kapetanovic MC, Saxne T, Nilsson JA *et al.* Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. Rheumatology (Oxford) 2007;46:608–11.
100. Mamula P, Markowitz JE, Piccoli DA *et al.* Immune response to influenza vaccine in paediatric patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2007;5:851–6.
101. Prevention CfDCA. Recommendations of the Advisory Committee on Immunization Practices: use of vaccines and immune globulins in persons with altered immunocompetence. MMWR Recomm Rep 1993, reviewed in 2004. CDC 2004 53:1–29.
102. Sands BE, Cuffari C, Katz J *et al.* Guidelines for immunizations in patients with inflammatory bowel disease. Inflamm Bowel Dis 2004;10:677–92.
103. Esteve M, Saro C, Gonzalez-Huix F *et al.* Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. Gut 2004;53:1363–5.
104. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. Am J Gastroenterol 2008;103:631–6.