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Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding☆

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Abstract

Background: Recommendations on breastfeeding under thiopurines are inconsistent due to limited data.
Aim: To assess the risk of infections in offspring breastfed by mothers receiving azathioprine (AZA) for inflammatory bowel disease (IBD).
Methods: Babies, who were breastfed from their mothers treated either with or without AZA were included from a local pregnancy-registry. Women were asked by structured personal interview on general development, infections, hospitalisations and vaccinations of their offspring.
Results: A group of 11 mothers taking AZA (median 150 mg/d) during pregnancy and lactation and another of 12 patients without using any immunosuppressive therapy breastfed 15 babies each for median 6 months and 8 months, respectively. Median age of children at time of interview was 3.3 and 4.7 years, respectively. All offspring showed age-appropriate mental and physical development. Infections were commonly seen childhood diseases. Similar rates were observed for most of the various infections between offspring with and without azathioprine exposure during breastfeeding. However, common cold more than two episodes/year and conjunctivitis were numerically more often reported in the group without AZA exposure. In an exploratory analysis no difference in the rate of hospitalisations was seen between exposed (0.06 hospitalisations/patient year) versus non-exposed children (0.12 hospitalisations/patient year, p=0.8)
Conclusion: Our study which reports the largest number of babies breastfed with exposure to AZA suggests that breastfeeding does not increase the risk of infections.

☆ The manuscript, including related data, figures and tables has not been previously published and the manuscript is not under consideration elsewhere.

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1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC), which are chronic inflammatory disorders, often become manifest in women of childbearing age.[1] Women are commonly concerned about the effect of inflammatory bowel disease (IBD) and medication on pregnancy and on the fetus. The management of women with IBD during pregnancy and breastfeeding should be performed in a multidisciplinary way, involving gastroenterologists, obstetricians, and pediatricians.[2]

Active disease, either at time of conception or during pregnancy, seems to be a risk factor of unfavorable birth outcome such as spontaneous abortion, stillbirths, preterm delivery, low birth weight, and developmental defects.[3,4] This underscores the importance of clinical remission before conception and of an established maintenance therapy during pregnancy. Azathioprine (AZA) and its metabolite, 6-mercaptopurine (6-MP), which are widely used for maintenance treatment in IBD patients, have recently been recommended for continued use in pregnancy.[2,4,5] Data of breastfeeding during immunosuppressive treatment are still scant though, and therefore this issue is being critically discussed in clinical practice. The US Food and Drug Administration (FDA) recommends against AZA in nursing mothers because of its potential for tumorigenicity.[6] Another reason why breastfeeding under AZA has been traditionally discouraged is the possible susceptibility to infections in neonates. However, according to the evidence based consensus of the European Crohn's and Colitis Organization (ECCO) breastfeeding during maintenance AZA treatment could be advised because only very small amounts of AZA/6-MP metabolites appear in breast milk.[2] Recently it has been shown that peak breast milk concentrations of 6-MP varying from 2 to 50 μg/L were measured only within the first 4 h after AZA intake with an estimated maximum exposure of drug to the infant of less than 1% of the maternal dose.[7] Additionally, neither 6-thioguanine nucleotides (6-TGN) nor 6-methylmercaptopurine nucleotides (6-MMPN) were detectable in the peripheral blood of the babies breastfed by mothers taking azathioprine.[8,9] However, the risks of bone marrow suppression, infections, and tumorigenicity to exposed children remain elusive due to lack of long-term assessment.

In the present study we determined if breastfeeding during maintenance AZA treatment in IBD patients is associated with a relevant risk of infections in the offspring.

2. Materials and methods

2.1. Patients and babies

Consecutive pregnant IBD patients, who attended our outpatient clinic between May 1999 and January 2007, were enrolled in our pregnancy-registry and regularly followed up every 3 months during pregnancy and every 3 to 6 months during lactation (Fig. 1). Eligible for inclusion into this study were babies breastfed by patients, who were taking AZA during pregnancy and lactation after appropriate counselling (group 1), and offspring breastfed by IBD patients without any immunosuppressive therapy (group 2, control group).

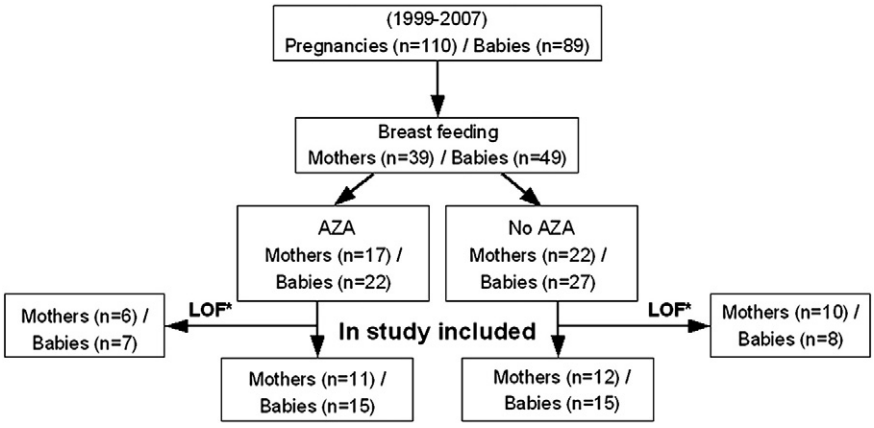
Diagnosis of IBD was based on clinical, radiological, endoscopic and histopathological criteria as recommended by ECCO.[10,11] For each patient disease specific data were collected (Table 1).

AZA and all other therapies of mothers were documented at each visit at our department.

The study was approved by the local ethics committee and women gave informed consent.

2.2. Questionnaire

Between November 2007 and October 2008 women were contacted by a single telephone call and asked in a form of a structured personal interview about their offspring regarding the mental and physical development, infections, hospitalisations and vaccinations. All of the babies had an adequate follow-up because in Austria babies have to be regularly examined by pediatricians according to the national guidelines ("Mutter-Kind-Pass").[12] These visits, which take place in week 1 and once between weeks 4 to 7, as well as once between months 3 to 5, 7 to 9, and 10 to 14, include the determination of height, weight and head circumference, physical examination, the assessment of general, motor skills and mental development, nutritional status, and the documentation of



Figuer 1 Consecutive pregnant IBD patients were enrolled in a pregnancy-registry. Their babies, who were breastfed either under AZA or without immunosuppressive therapy, were included in this study. *LOF = Loss of follow-up.

Table 1 Characteristics of study population.

	AZA during breastfeeding	No AZA during breastfeeding
No. of IBD patients (CD/UC)	11(11/0)	12 (5/7)
Age at delivery, year, median (range)	30 (21–41)	31 (23–38)
Age at diagnosis, year, median (range)	19 (15–28)	24 (15–30)
Intestinal resections, n (%)	9 (81.8)	2 (16.7)
Smokers, n (%)	1 (9.1)	1 (8.3)
Concomitant medication, n (%)		
No medication	9 (81.8)	9 (75)
Probiotics	0	3 (25)
5-ASA, sulphasalazine	2 (18.2)	4 (33.3)
No. of neonates (female/male)	15 (6/9)	15 (5/10)
Birth length, cm, median (range)	51 (46–53)	51 (46–53)
Birth weight, g, median (range)	3480 (2076–4400)	3310 (2010–4010)
Prematurity (<37 weeks)	1	3
Low birth weight (<2500 g)	1	3
Duration of breastfeeding, months, median (range)	6 (1–18)	8 (3.5–23)
Follow-up, years, median (range)	3.3 (0.6–6)	4.7 (1.1–8.6)

diseases. General development is checked by growth and body mass index (BMI) charts according to percentile curves. Motor skills are examined by small exercises, e.g. movements of head and chest in a ventral position, grasping movements, crawling, ability to sit/stand up straight and to go. Mental status is assessed by reactions to various stimuli (e.g. movements, light, noise, and name) and language development. Additionally, an orthopaedic (week 1 and weeks 4 to 7), ophthalmological (months 10 to 14) and an ear, nose and throat examination (months 7 to 9) are performed. In addition to the entries retrieved from the "Mutter-Kind-Pass" information on the health status of the children was collected from diaries kept by the mothers on her children, medical records, and the mothers' memory.

2.3. Statistical analysis

All results are expressed as absolute numbers and percentages. Descriptive statistics were to be presented for the rate of infectious diseases between offspring breastfed by mothers with or without azathioprine treatment. An exploratory analysis was performed on the rate of hospitalisation due to infections as most stringent outcome between group 1 and group 2 by means of Cox regression. Differences were considered to be significant if $p<0.05$. Calculations were done by the SPSS statistical software (Release 14.0, 2005; SPSS Inc., Chicago, IL).

3. Results

3.1. Patient and baby characteristics

A total of 30 babies, who were delivered by 23 IBD patients, were enrolled in the study (Fig. 1). CD and UC were diagnosed in 16 and 7 patients, respectively. AZA treatment, which was started median 5.6 years (range: 2.5–9.2 years) prior breastfeeding, was used in 11 women and dosage, which was adapted to the patient's body weight, was given once a day in the morning (median dose 150 mg/d; range: 100–250 mg/d). Twelve patients received no immunosuppressive therapy during pregnancy and lactation. Median duration of pregnancy in patients under AZA was 38.5 weeks (range: 36–40 weeks) and in subjects without exposure to AZA 39 weeks (range: 32–40 weeks).

In 8 patients concomitant IBD medication was applied during lactation (Table 1). None of the patients was in need of systemic steroids or budesonide for control of symptoms of IBD during breastfeeding.

The median time of breastfeeding in group 1 (n=15) and group 2 (n=15) was 6 months (range: 1–18 months) and 8 months (range: 3.5–23 months), respectively. Median age of children at time of interview was 3.3 (range: 0.6–6 years) and 4.7 years (range: 1.1–8.6 years), respectively.

3.2. General development and vaccinations

All of the neonates were regularly examined by pediatricians according to the national guidelines. Age-appropriate mental and physical development were confirmed in all of the offspring. Vaccinations according to the national recommendations for neonates were administered to all of the babies, none of them came down with one of these respective diseases.[13]

3.3. Infections

All infections recorded were childhood diseases as commonly seen in the general population. Similar rates were observed for most of the various infections between offspring breastfed by mothers with or without azathioprine treatment (Fig. 2). However, more than two episodes of common cold per year were numerically more often reported in babies breastfed by mothers without immunosuppressive therapy (9 versus 1). Conjunctivitis was observed in 6/15 (40%) offspring of group 2 compared to one baby (6.7%) nursed under maintenance AZA treatment, who suffered from a stenosis of the tear duct.

3.4. Hospitalisation

Hospitalisation was reported in 6 and 9 children of group 1 and group 2, respectively. Furthermore, 6 children nursed by

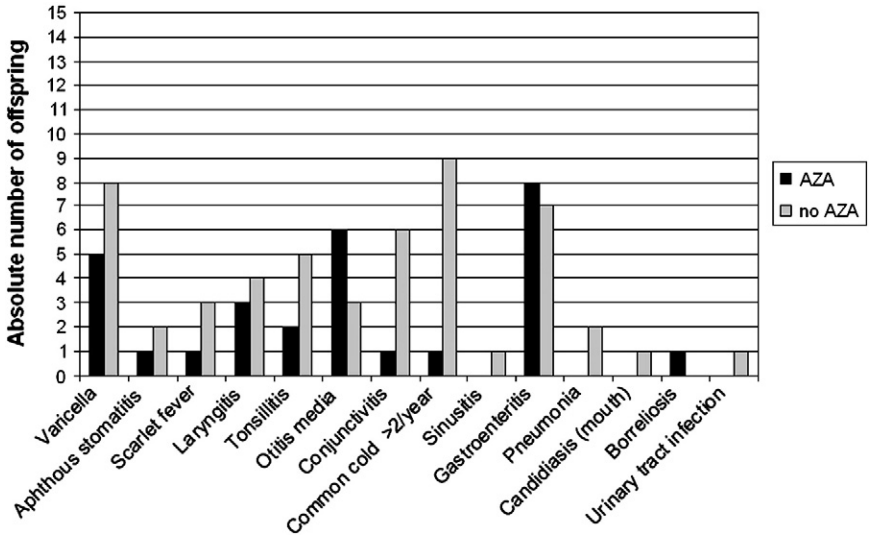


Figure 2 Absolute number of children with various infectious diseases. n=15 in each group; AZA=children breastfed by mothers under maintenance AZA treatment, no AZA=children breastfed by mothers without maintenance AZA treatment; median observation period in AZA=3.3 years, in no AZA=4.7 years. Given are children with at least one event, excepting for common cold for which children with >2 events are shown.

mothers without AZA required more than one hospitalisation, but none in group 1. Reasons for hospitalisation are shown in Table 2. The number of children with a hospitalisation due to an infection appeared higher in babies of mothers without exposure to AZA (Fig. 3). In an exploratory analysis no difference in the rate of hospitalisations was seen between group 1 (0.06 hospitalisations/patient year) and group 2 (0.12 hospitalisations/patient year, p=0.8).

3.5. Other diseases

Neurodermatitis was diagnosed in 3 and 4 of children of group 1 and group 2, respectively. One baby breastfed by a mother without immunosuppressive therapy suffered from lactase deficiency syndrome. Allergy was reported in 2 infants of the same group. No malignant disease was observed in any child.

Table 2 Reasons for hospitalisations.

	AZA during breastfeeding, n (%)	No AZA during breastfeeding, n (%)
Gastroenteritis	3 (20)	3 (20)
Tonsillectomy/ adenoidectomy	2 (13.3)	1 (6.7)
Pneumonia/ bronchitis	0	3 (20)
Phimosis	0	3 (20)
Hydrocele testicular	0	1 (6.7)
Urinary tract infection	0	1 (6.7)
Abscess	0	1 (6.7)
Burn	0	1 (6.7)
Frenotomy	0	1 (6.7)
Suspected respiratory standstill	0	1 (6.7)
Persistent ductus botalli	1 (6.7)	0

4. Discussion

Data on the long-term outcome of babies breastfed by mothers while taking AZA for IBD are lacking. In our study we followed children of such a potential risk profile for a median of 3.3 years and compared their outcome to nursed children from mothers with IBD not exposed to AZA during pregnancy and lactation. We did not find numerical differences in the rates of infections among the offspring of both groups.

The World Health Organization (WHO) promotes exclusive breastfeeding as the best form of alimentation for newborns in the first six months of life.[14] Human milk contains a balanced nutrient composition, which is important for tissue

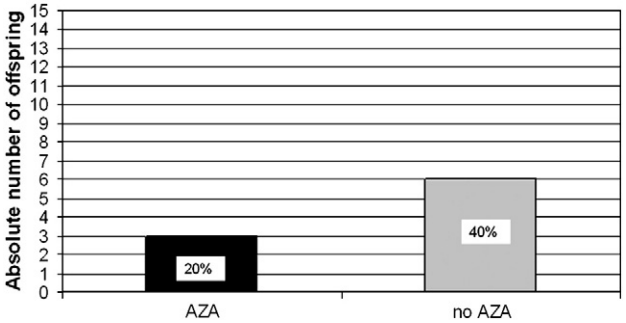


Figure 3 Absolute number of children hospitalised due to infections. n=15 in each group; AZA=children breastfed by mothers under maintenance AZA. Treatment, no AZA=children breastfed by mothers without maintenance AZA. Treatment; median observation period in AZA=3.3 years, in no AZA=4.7 years.

growth and development in babies. Furthermore, a complex mixture of defense agents is detectable in breast milk, which are divided into antimicrobial agents, anti-inflammatory factors, immunomodulators, and leukocytes and associated with health benefits for the newborns.[15,16] Nursing protects infants from common childhood diseases, e.g. gastroenteritis, otitis media and respiratory infections.[17,18] According to the literature breastfeeding also confers long-term benefits for the children. Protective effects against later obesity, arterial hypertension, and hypercholesterolemia were reported.[19] Breastfeeding, which may enhance the development of an infant's immune system, is even associated with a lower risk for immune-related diseases, such as type 1 diabetes, coeliac disease and IBD.[19,20] Furthermore, a recent paper suggested that breastfeeding may have a protective role in prevention of further flares in IBD patients.[21] In addition to these health advantages nursing also offers a social benefit by intensifying the mother–child relationship. Despite these well-established positive effects of breastfeeding, women taking AZA have yet been discouraged from nursing because of the theoretical risks of infections and tumorigenicity in offspring.[6]

6-MP was detectable in some breast milk samples from women on standard doses of AZA, but concentrations were much lower than in the serum and did not achieve a therapeutic immunosuppressant serum level.[7,9,22] Christensen et al. reported that compared to peak plasma levels of 6-MP, which were measured within 3 h after drug administration, the major part of 6-MP in breast milk was excreted within the first 4 h after AZA intake and decreased at least after 5 h.[7] Due to this observation the authors suggested that women should use a breast pump 4 h after AZA intake to discard the first portion of milk produced after drug ingestion to reduce the infant's drug exposure. However, concentrations of active metabolites of azathioprine (6-TGN and 6-MMP) were always below the detection limit in the peripheral blood of babies breastfed by mothers taking AZA.[8,9]

Data regarding development of the offspring from mothers under treatment with AZA during lactation are mostly restricted to small series from organ transplantation. No clinically overt adverse events were noted, despite the additional concomitant immunosuppressive therapy of mothers in the posttransplant setting.[8,9,23,24] However, these observations were limited to the period of lactation. In our study babies exposed to AZA were followed for median 3.3 years. On all offspring normal age-related mental and physical development was reported. Infections were childhood diseases as commonly seen in the general population and there were similar rates of most infectious diseases between offspring breastfed by mothers with or without exposure to azathioprine. Only common cold disease with more than two episodes per year and conjunctivitis were numerically more often reported in babies breastfed by mothers without immunosuppressive therapy. In an exploratory analysis no difference in hospitalisations due to infections per year was observed between these groups. Furthermore, the hospitalisation rate of 0.07 in children aged under 1 year and exposed to AZA in our study is in line with the rate of 0.07 reported from a US nationally representative database.[25] The numerical higher number of hospitalisations due to infections among non-exposed children could be explained by a higher proportion of preterm babies and/or a longer follow-up as the risk for infectious diseases increases with contacts to other children, particularly from entry in the day nursery or kindergarten.

Our study is limited by the small sample size of children in both groups, as well as the fact that no formal matching procedure has been performed. Thus, robust conclusions on a non-inferior risk of infections in AZA exposed children cannot be drawn. The same applies for a potential tumorigenicity of thiopurines in young children, for which duration of follow-up in our study might even be too short to capture major events. No single malignant disease was observed in our study. Nevertheless, we need to stress that our cohort reports the largest number of babies ever breastfed during AZA treatment. Our results might help to design a prospective study necessitating the inclusion of hundreds of children in both groups.

In conclusion, our data suggest that there is no increased risk of infections in babies born to mothers exposing their babies to azathioprine in utero and via breastfeeding. Therefore, our data support a current recommendation from the evidence based consensus of ECCO that breastfeeding under maintenance AZA treatment could be advised to women who wish to nurse their infants.[2] However, mothers should be counseled to use a breast pump 4 h after medication intake to discard the first portion of milk produced after AZA intake in order to minimize the infant's exposure.[7]

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SA: clinical investigator, data collection, statistical analysis, data interpretation, and manuscript writing.

WR: conception and design of the study, clinical investigator, data interpretation, and critical revision of the manuscript.

AM: data interpretation and critical revision of the manuscript.

WM: clinical investigator and statistical analysis.

GN: clinical investigator and critical revision of the manuscript.

HV: clinical investigator and critical revision of the manuscript.

CD: conception and design of the study, data collection, data interpretation, and study supervision.

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