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REVIEW ARTICLE

Pregnancy in patients with immune-mediated inflammatory diseases

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Abstract

A large percentage of patients with immune-mediated inflammatory diseases (IMIDs) are women of childbearing age. Pregnancy is a complex physiological scenario and causes significant endocrine and immunological changes. Pregnancy can trigger a worsening of IMIDs and, bidirectionally, disease flares are associated with worse pregnancy outcomes. This highlights the importance of achieving adequate control of IMIDs before conception and during pregnancy. When choosing pharmacological therapy in pregnant women with IMIDs, it is important to be aware of all available options and their potential impact on the mother and fetus. The aim of this review is to highlight the influence of pregnancy on the clinical evolution and prognosis of the most common cutaneous, rheumatological, and gastroenterological IMIDs. In addition, we provide an updated review of the different systemic and topical therapies used for the treatment of common dermatoses (such as atopic dermatitis, psoriasis, and hidradenitis suppurativa) and their safety profile during pregnancy and lactation.

Keywords: *Inflammatory disorders. Pregnancy. Breastfeeding. Therapy. Outcome.*

Introduction

Immune-mediated inflammatory diseases (IMIDs) are characterized by a female preponderance and usually debut during a woman's reproductive years. Thus, they are among the most common pre-existing diseases in pregnancy. The course of the disease can be highly variable during pregnancy, ranging from symptom improvement to exacerbations of the disease, leading to maternal and fetal complications. Associated obstetric complications often include variably increased rates of miscarriage, intrauterine fetal death, fetal growth retardation, and preterm delivery.

Given that women with IMIDs have potentially high-risk pregnancies, it is important to seek the most effective and safe drug profile possible during this period to optimize outcomes. When choosing drug therapy in pregnant women with IMIDs, it is important to be aware of all available options and their potential impact on the mother and fetus.

However, the use of systemic immunosuppressive drugs in pregnant women can be challenging. Some of the systemic drugs prescribed in the treatment of IMIDs are potentially teratogenic, while, for others, there is insufficient experience of use in human pregnancies and their potential impact on fertility, pregnancy, fetal, and neonatal development is not fully understood. The evidence is mainly based on observational studies and is often limited.

The aim of this review is to highlight the impact of pregnancy on the clinical evolution and prognosis of the most common cutaneous, rheumatological, and gastroenterological IMIDs. Although these diseases share several therapeutic options, in this review, we will focus on the safety profile during pregnancy and lactation of the different systemic and topical therapies used for the treatment of atopic dermatitis (AD), psoriasis, and hidradenitis suppurativa (HS).

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Cutaneous IMIDs

Atopic dermatitis

AD is the most common skin disorder during pregnancy and usually debuts during the second or third trimester. During gestation, the immune system is biased toward a T helper 2 (Th2)-dominated immune response, with the goal of inducing tolerance in the fetus. Because AD itself is a Th2-driven disease, women with AD are at increased risk of experiencing disease flares during pregnancy[1].

The previous studies have shown that about 25% of women with AD improve during pregnancy, while more than 50% have a worsening of disease symptoms, with worsening occurring most frequently in the second or third trimester of pregnancy (Table 1)[2,3].

Contrary to the tendency of AD to worsen during pregnancy, a study involving 10,441 pregnancies of women with AD revealed a pattern of increased use of topical corticosteroids (TCS) and ultraviolet (UV) light treatment, concomitant with decreased use of topical calcineurin inhibitors (TCI), and systemic treatments, compared to pre-pregnancy use. This may reflect a tendency for women to endure more DA flares during pregnancy, combined with a more cautious, and restricted treatment approach[1].

However, under-treated AD could negatively affect maternal well-being and fetal development, so careful risk-benefit assessment and choice of appropriate treatment during pregnancy are necessary. The social isolation effect of AD and its physiological impact on fertility has not been fully investigated. Some data from the literature suggest that the systemic inflammation found in patients with asthma may affect the uterine mucous layer (decidua) and thus impair effective implantation of the embryo[4]. For other atopic diseases, such as AD, this relationship with reduced fertility is less clear[4].

Similarly, studies focusing on potential pregnancy complications directly related to AD are scarce. Neonatal staphylococcal septicemia, eczema herpeticum, and premature rupture of membranes are currently the only reported complications that are significantly increased in pregnant patients with AD[1]. To date, no evidence of increased rates of infertility, prematurity, low birth weight, miscarriage, stillbirth, or congenital malformations has been found in this population (Table 1)[2,3].

Therapeutic guideline recommendations for atopic dermatitis in pregnant patients

Topical treatment

Emollients, TCS, and TCI are the first-line treatments for pregnant women with AD and are considered safe treatments before conception and during pregnancy and lactation (Fig. 1)[5].

The treatment with potent or very potent TCS has been associated with an increased risk of low birth weight when the total dose exceeds 300 g throughout pregnancy[6,7]. There is no increased risk of preterm birth or malformations associated with TCS use during gestation[6,7].

Fetal exposure depends on the steroid used: non-fluorinated steroids (prednisolone and methylprednisolone) are metabolized in the placenta by the enzyme 11-beta-hydroxysteroid dehydrogenase, whereas fluorinated steroids (betamethasone and dexamethasone) are metabolized at a much slower rate. In addition, fluticasone propionate is the only TCS that should not be used during pregnancy, as it crosses the placental barrier without being metabolized and can, therefore, reach the fetus in high concentrations[6,7].

However, if the amount of TCS used exceeds 200 g/month, treatment may reach systemic exposure levels, which indicates poorly controlled disease and is considered a risk factor. In this case, as an alternative to increasing the dose, a second drug to complement the main drug, or a therapeutic escalation to phototherapy should be considered[5].

Furthermore, due to the side effect of TCS in decreasing dermal elasticity and thus increasing the risk of stretch marks development, alternative topical treatments, such as TCI, may be considered in susceptible areas (face, intertriginous areas, or thighs).

On the other hand, there are no studies on the use of TCI during pregnancy; however, oral tacrolimus has been widely used in pregnant women after solid organ transplantation, with no observed teratogenic or mutagenic effects[8]. Although an increased risk of prematurity has been demonstrated, it may be associated with baseline maternal disease[8]. In addition, systemic absorption of TCI, due to the large size of the molecules, is negligible and no tendency for their accumulation has been found.

Phototherapy

Narrowband UVB (NB-UVB) and UVA1 phototherapy are considered second-line treatment in pregnant patients with AD who do not respond to topical treatments[5].

Table 1. Summary of available information regarding IMIDs clinical course during pregnancy and influence on maternal/fetal outcome

Inflammatory disorders	Disease course during pregnancy	Pregnancy outcome*
Atopic dermatitis	Worsening likely	Generally uneventful
Psoriasis	Improvement likely	Generally uneventful
Hidradenitis suppurativa	Worsening likely but controversial findings	Poor outcome likely
Rheumatoid arthritis	48-60% improvement, 40% stabile or worse	Poor outcome likely
Systemic lupus erythematosus	Worsening likely, especially if active disease or < 6 months' remission	Poor outcome likely, especially if active disease or < 6 months' remission
Inflammatory bowel disease	A third of patients develop flare activity	Poor outcome likely, especially if active disease or < 6 months' remission

*The table illustrates the information in brief, please consult the text for details. IMIDs: immune-mediated inflammatory diseases.

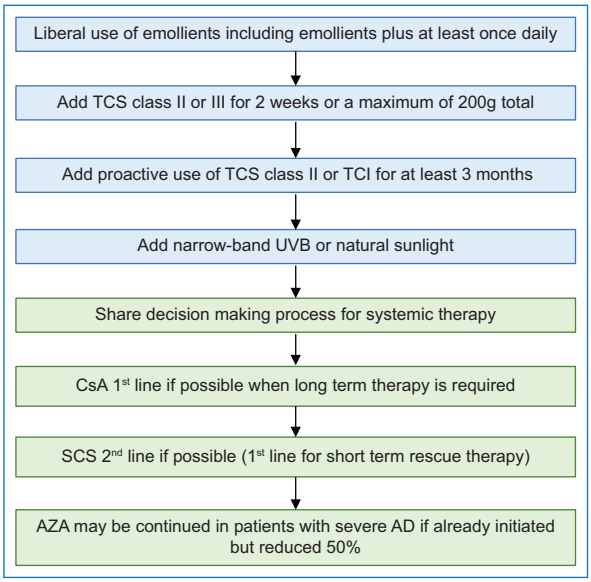

Figure 1. Algorithm for the treatment of pregnant women with atopic dermatitis[5].

UVB radiation is not considered teratogenic and can be used during pregnancy. However, pregnant women are at increased risk of developing melasma after UV exposure[5]. There is also evidence that UVB therapy can decrease serum folic acid levels, and this should be monitored at least once per trimester and compensated with folic acid supplementation (0.5-0.8 mg/day) before conception and during pregnancy[5]. In contrast, psoralen is not recommended preconceptionally (3 months) or during pregnancy due to its potential mutagenic effect[5].

Classical systemic therapy

Classical systemic therapy is the next therapeutic step if the disease cannot be controlled with topical treatment and UV therapy (Fig. 1).

Systemic corticosteroids

Systemic corticosteroids (SCSs) are occasionally used in non-pregnant AD patients as short-term treatment in acute and severe flares. Long-term use is not recommended due to serious side effects, including osteopenia, osteoporosis, type 2 diabetes, high blood pressure, glaucoma, infections, adrenal suppression, stretch mark formation, acne, and others[5]. During pregnancy, SCS may also increase the risk of gestational diabetes, pre-eclampsia, and even premature rupture of membranes and preterm delivery[5]. Studies of SCS use during pregnancy have not shown increased risk of teratogenicity, but repeated courses of treatment may result in decreased birth weight and increased incidence of gastrointestinal reflux in neonates[9]. The previous studies have suggested an increased risk of cleft palate in newborns when the mother was treated with SCS during pregnancy; however, this association was not confirmed in a later Danish cohort study involving 1449 women who used inhaled or oral corticosteroids before conception or during the first trimester of pregnancy[10].

Although the current literature shows that there appears to be no evidence of prolonged neonatal adrenal suppression in mothers treated with SCS during pregnancy, some studies recommend that infants born to mothers treated with > 35 mg/day of prednisolone should maintain an observation period of 48 h[11]. On the other hand, SCS treatment during lactation is safe, as < 0.1% of the dose ingested by the mother is excreted in breast milk[5].

SCS treatment appears to be safe in pregnant women provided that the mother and newborn are adequately monitored. The latest guidelines of the European Task Force on Atopic Dermatitis (ETFAD) recommend that the use of systemic glucocorticoids in patients with AD should be restricted to short-term treatment (< 2-3 weeks),

only if TCS and UV therapy has failed, and that the daily dose should not exceed 0.5 mg/kg/day[5].

If SCS treatment is needed in pregnant patients with AD, prednisolone, not dexamethasone, should be used[5].

Cyclosporin A

There is abundant evidence on the safety of cyclosporin A (CsA) use in pregnancy from studies focusing on patients with solid organ transplantation or systemic autoimmune diseases.

CsA crosses the placenta and the fetal serum concentration is up to 64% of the maternal concentration. A slightly increased risk of preterm birth and low birth weight has been demonstrated in newborns of mothers exposed to the drug during gestation; however, this could be attributed to the patients' underlying diseases. No teratogenic or mutagenic effects or fetal death associated with its use have been observed[5]. CsA is excreted in breast milk and can be transmitted to the fetus[5]. However, most publications indicate that breastfeeding is safe and that the amount ingested by the infant has no adverse effects, although monitoring of serum CsA concentrations in the newborn is currently recommended[5].

However, possible impairment of renal function or the development of high blood pressure is common side effects, and therefore, these parameters should be closely monitored during pregnancy. Based on these data, CsA can be used during the preconception period, pregnancy, and lactation in special cases, when the maternal benefit justifies the potential risk to the fetus. ETFAD classifies CsA as first-line systemic treatment during pregnancy when long-term systemic therapy is required for adequate disease control[5].

Azathioprine

Azathioprine (AZA) is most commonly used to treat inflammatory bowel disease (IBD) and other autoimmune diseases (such as systemic lupus erythematosus), but, in many countries, it is used off-label as an immunosuppressant to treat AD and is considered a treatment option for pregnant women with severe AD[5].

Evidence for AZA use during pregnancy comes from studies in patients with IBD. No teratogenic or mutagenic effects on the fetus have been observed, but it does seem to be associated with an increased risk of preterm delivery[12]. Maternal intake does not lead to immunosuppression in infants, and the rate of infection and hospitalization is not increased in children exposed to AZA *in utero* or through breastfeeding when followed up at 3 years of age[13].

Therefore, AZA can be used off-label for patients with AD before conception, during pregnancy and lactation, in isolated cases, when topical therapy, UV, and CsA treatment have failed, are not tolerated or are contraindicated for any reason[5]. Close monitoring by an experienced obstetrician is strongly recommended when prescribing this drug during pregnancy.

Methotrexate

Methotrexate (MTX) is used off-label for the treatment of severe AD in non-pregnant patients when other systemic drugs have been ineffective. MTX does not decrease the chances of conception[14]. However, the drug is teratogenic and contraindicated during pregnancy.

Because MTX blocks DNA synthesis, the drug is associated with severe birth defects, including craniofacial anomalies, limb defects, cardiovascular defects, genital defects, and mental retardation when administered during pregnancy[14]. Even low-dose exposure (< 20 mg/week) can cause birth defects[14]. Therefore, in cases of inadvertent exposure during pregnancy, termination of pregnancy is not warranted, but the treatment should be stopped immediately and ultrasound should be offered to examine fetal development[14].

In breastfeeding, MTX is excreted in breast milk, but at concentrations of < 10% of maternal serum concentrations. Since even these low doses have been found to cause immunosuppression and neutropenia in infants, MTX treatment during lactation is discouraged[14]. The European League Against Rheumatism (EULAR) working group recommends discontinuing MTX 1-3 months before conception in planned pregnancies[15], while the European Medicines Agency (EMA) establishes a recommended drug washout period of up to 6 months before conception.

Mycophenolate mofetil (MMF)

MMF prevents DNA synthesis by inhibiting purine synthesis through blockade of the enzyme inositol monophosphate dehydrogenase. MMF is teratogenic and is associated with a high rate of spontaneous abortions and a cluster of specific embryonic malformations known as MMF embryopathy, including microtia, aural atresia, cleft lip and palate, hypertelorism and polydactyly, as well as abnormalities in the central nervous system (CNS), renal, and cardiovascular systems[16]. There are no data on the consequences of MMF use in lactating women; however, it is secreted into milk, so breastfeeding is not recommended during MMF treatment. There are currently no studies on its impact on fertility[16].

MMF is absolutely contraindicated in patients with AD during preconception, pregnancy, and lactation and also in male patients with AD with reproductive desire, until at least 3 months before conception[5].

Biological therapy

Information on the use of biologics for the treatment of atopic disorders during pregnancy is limited in humans[4]. This causes great uncertainty in clinical decision-making when adequately treated women with good therapeutic response to biologics plan to conceive or become pregnant. The treatment is often discontinued due to lack of safety data.

At present, the body of evidence is restricted to small observational studies and case reports, and information on the safety of biologics in pregnancy comes mainly from extrapolation of studies in patients with IBD and rheumatological diseases. Although atopic diseases are among the most common diseases of reproductive age, there is a lack of research and information on the pharmacokinetics and, more importantly, on the safety of these treatments.

Dupilumab

Dupilumab is a fully humanized IgG4 monoclonal antibody directed against the alpha subunit of the interleukin (IL)-4 receptor, blocking both the IL-4 and IL-13 signaling pathways. It is currently approved for the treatment of severe AD, severe asthma, and chronic rhinosinusitis with nasal polyposis.

There are no studies to date on fertility, pregnancy complications, embryotoxicity, or breastfeeding consequences. Animal studies have not indicated direct or indirect harmful effects on fertility or adverse effects on their offspring[17]. To date, only two case reports of patients who maintained dupilumab during pregnancy have been published: one patient who maintained dupilumab throughout pregnancy and lactation; and the other patient who started dupilumab treatment at 24 weeks gestation due to an AD flare with poor response to other treatments. In both cases, no fetal or maternal complications were reported[18,19]. However, the current experience is anecdotal.

Human IgG antibodies are known to cross the placental barrier; therefore, this drug may be transmitted from the mother to the developing fetus. IgG levels in the fetal circulation increase after week 13, reaching 50% at weeks 28 to 32, and may exceed maternal levels after week 35[4]. In addition, among the different types of immunoglobulins, IgG4, in particular, is transported across the placental barrier at a high rate (IgG1 > IgG4 > IgG3 > IgG2). Due to the immature reticuloendothelial system, it has been proposed that there is reduced clearance of biologics in infants[4].

In general, contraception should be maintained during therapy. Due to the paucity of safety data available on the potential complications of dupilumab treatment during pregnancy and the consequences of exposure to the fetus, dupilumab is currently not recommended before conception or during pregnancy or lactation[4].

Tralokinumab

Tralokinumab is a new anti-IL-13 antibody recently approved by the Food and Drug Administration (FDA) and EMA for the treatment of severe AD in 2021.

There are no published data on its use in pregnant women, nor has the necessary washout period before conception been specified[20]. Prenatal and postnatal studies with tralokinumab in monkeys have not identified adverse effects on mothers or their offspring up to 6 months postpartum. However, because its effects in humans are unknown, it is recommended that tralokinumab use during pregnancy be avoided as a precautionary measure[20].

JAK inhibitors

A number of novel therapies are now available for the treatment of AD. Baricitinib is the first Janus kinase (JAK) inhibitor that has been approved by the FDA and EMA for the treatment of severe AD in adult patients[21]. It is a small molecule that inhibits both JAK1 and JAK2[21].

Very limited data are available on the safety of JAK inhibitors in pregnancy and on female fertility. Reproductive toxicology studies have shown no adverse fetal effects in animals exposed to baricitinib at twice the approved human concentration. However, at concentrations approximately 10-39 times the human label dose, a reduction in fertility and a teratogenic effect, with decreased fetal growth and weight and skeletal malformations have been observed, respectively, in rats and rabbits[21]. There are no data on the impact of its use during lactation and it is unknown whether it can be transferred to human milk[21].

Based on these findings, baricitinib is contraindicated in pregnancy and during lactation, and women of childbearing age are advised to use effective contraception during and at least 1 month after treatment[22]. To date, one case has been reported of maternal exposure to baricitinib during pregnancy, preconceptionally, and

during the first trimester up to 17 weeks of gestation, in a patient with rheumatoid arthritis (RA), resulting in a healthy full-term infant[21].

The other JAK inhibitors recently approved by the FDA and EMA for the treatment of severe AD, upadacitinib, and abrocitinib, are also contraindicated during pregnancy. Both drugs are elective oral JAK1 inhibitors and were developed with the aim of improving the safety profile by minimizing the effects of blockade on JAK3 and JAK2[23].

Although there are no data on their effects in pregnant women, embryofetal development studies in animals have shown them to be teratogenic in rats and rabbits. At human doses (15 and 30 mg), upadacitinib caused increased skeletal malformations and increased rate of post-implantation abortions in rats and cardiovascular malformations in rabbits[23]. Regarding abrocitinib, to date, no data on its effects on fertility, fetal development, pregnancy, and lactation have been reported. Therefore, the data for both products recommend that women of childbearing age use effective contraception during treatment and for 4 weeks after the final dose of upadacitinib and abrocitinib.

Psoriasis

Psoriasis is a chronic IMID that affects 1-3% of the world's population[24]. The prevalence is similar in men and women, and the disease usually debuts before the age of 40[24]. Therefore, in routine clinical practice, a large percentage of patients with psoriasis managed by dermatologists are women of childbearing age[24].

The course of psoriasis may fluctuate throughout pregnancy as hormone levels change. The current literature points to a trend toward an improvement in the clinical course of the disease during pregnancy, with a slight risk of exacerbations after delivery. It has been reported that approximately 55% of patients have an improvement of the disease during pregnancy, 21% remain stable, and 23% of women experience an exacerbation of psoriasis (Table 1)[24].

After delivery, the proportion changes: approximately 9% of patients show improvement; 26% remain stable; and 65% experience a worsening of their disease, with most returning to their pre-pregnancy baseline level of activity[24]. In addition, psoriasis is associated with other problems, such as the potential impact of anti-psoriatic treatments and the disease itself on fertility or the possible involvement of localized disease in the nipple and breast area, making breastfeeding difficult[24].

Regarding fetal impact, psoriasis, particularly uncontrolled disease, has been associated with adverse outcomes such as low birth weight neonates, preterm delivery, pre-eclampsia, small-for-gestational-age fetuses, and fetal loss[24]. However, this association between psoriasis and adverse pregnancy events remains unclear at present and is the subject of recent publications. The study by Tsao *et al.*[25] shows that underlying conditions are important features to consider as potential confounders for pregnancy outcomes. Gestational risk factors such as obesity, dyslipidemia, depression, diabetes, and hypertension should be excluded, and the fact that these comorbidities are often associated with psoriasis may be a confounding bias in adverse pregnancy outcomes. Therefore, it is likely that the negative impact on fetal development is due to maternal baseline comorbidities or drug exposure, rather than direct and potentially harmful psoriasis-related inflammation (Table 1)[25].

Therapeutic guideline recommendations for psoriasis in pregnant patients

During pregnancy, the treatment with low-to-moderate potency topical steroids is recommended as first line and narrowband ultraviolet B phototherapy as second line therapy in limited disease (Fig. 2)[26]. It is advised that psoriasis be controlled or in remission before conception to minimize possible flares during pregnancy[27,28].

However, in patients with severe disease, there may be a strong need to continue or introduce systemic therapy. Among the available classical systemic treatments, methotrexate, acitretin, and other systemic retinoids are teratogenic and contraindicated during pregnancy (FDA category X). It is also recommended to discontinue treatments with systemic PUVA (psoralen and ultraviolet A), apremilast, and dimethyl fumarate due to their potential teratogenic effects. Therefore, only cyclosporine and systemic steroids (in the second and third trimester) can be used in pregnant patients after appropriate risk-benefit counseling (FDA category C)[27,28]. Specific treatment with biologics, despite having revolutionized the natural history of the disease, is not generally recommended during the preconception period, pregnancy, and lactation due to the lack of clinical safety trials.

Detailed information on the potential impact on pregnancy of classical systemic psoriasis drugs is discussed in the AD and HS treatment sections.

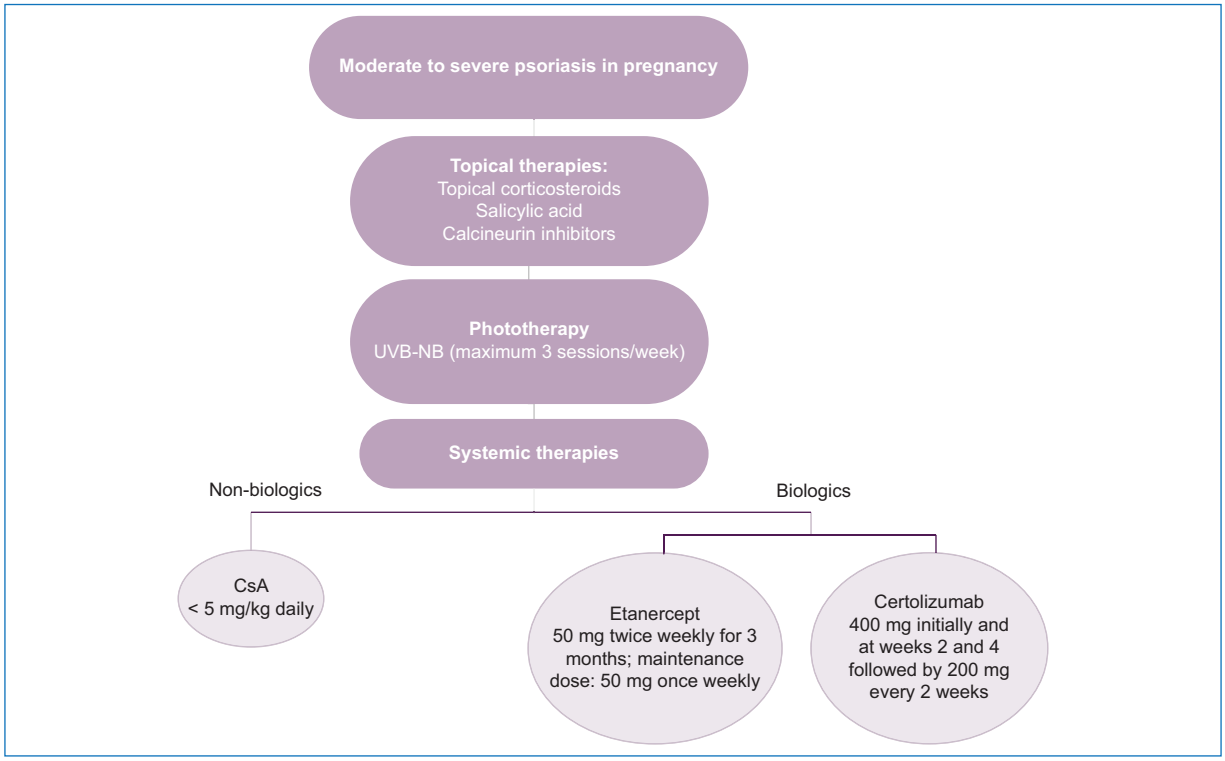

Figure 2. Algorithm for the treatment of pregnant women with psoriasis *(modified from Timis et al. 2021)*[26].

Biologic therapy

Biologics currently approved by the FDA and the EMA for the treatment of moderate-to-severe psoriasis are classified into the following groups: tumor necrosis factor (TNF)-α inhibitors (infliximab, adalimumab, etanercept, and certolizumab pegol), interleukin (IL)12 and IL23 p40 monoclonal antibodies (ustekinumab), anti-IL17A antibodies (secukinumab, ixekizumab, and brodalumab), and IL23 p19 subunit inhibitors (guselkumab, risankizumab, and tildrakizumab).

Most of these drugs are IgG monoclonal antibodies and are actively transported across the placenta through the Fc receptors of the syncytiotrophoblast and cannot cross the placenta by simple diffusion due to their size (> 100 kDa). It is thought that, due to the absence of Fc receptors in the first trimester, there is no fetal exposure to biologic drugs during early embryogenesis and the risk of teratogenicity is low[27,28].

As exceptions, etanercept (fusion protein) has lower affinity for placental Fc receptors, and reduced or no placental transfer has been reported for certolizumab pegol (pegylated human IgG1 monoclonal antibody), as it lacks an Fc receptor[27,28]. Given its molecular structure, certolizumab pegol is considered the most appropriate anti-TNF for use during pregnancy and lactation.

At present, decision-making about continuing or initiating biologic therapy in pregnant patients remains complex due to limited knowledge about the long-term safety of intrauterine exposure. PSOLAR[29], a multicenter observational registry evaluating pregnancy outcomes of women with psoriasis who received biologic therapy during gestation or the prenatal period, reported that rates of miscarriage, neonatal problems, and congenital malformations were similar to those of the general US population.

However, there are conflicting results in the literature. Three systematic reviews[30-32] from 2018, 2019, and 2021 reported that pregnant women with chronic inflammatory diseases (including psoriasis) exposed to anti-TNFα therapy had an increased risk of congenital malformations, small-for-gestational-age fetuses, neonatal infections, and preterm pregnancies. A subsequent meta-analysis[25], which included studies with adjusted odds ratios, did not show an increase in congenital malformations associated with biologic use in pregnant women with chronic inflammatory diseases, suggesting that adverse effects may

be due to disease activity or other confounding factors.

Another important aspect to consider is the possibility of an altered immune response in newborns of patients who continue treatment with biologic agents during the past months of pregnancy and, in particular, until the third trimester[27,28]. The Centers for Disease Control and Prevention (CDC) recommends, given the rate of placental transmission of antibodies during the second and third trimester of gestation, postponing the administration of attenuated vaccines during the first 6 months of life to newborns born to mothers who continue treatment with monoclonal antibodies after 20 weeks of gestation, because an increased risk of infections due to neonatal immunosuppression and even fatal cases, such as a disseminated BCG (Bacillus Calmette-Guerin) infection in a newborn whose mother had been treated with infliximab for Crohn's disease, has been reported[33]. Inactivated vaccines can be administered according to CDC-recommended guidelines.

Current guidelines from Psoriasis Group of the Spanish Academy of Dermatology and Venereology, EMA, and British Association of Dermatologists 2020 recommend preconception counseling and advocate the use of contraception in women of childbearing age receiving biologic therapy as long as pregnancy is not contemplated or when it is preferable to postpone pregnancy. It is advisable to interrupt, if possible, biologic treatment in the second and third trimester to minimize exposure and fetal risk[27,34]. If clinically necessary, the use of anti-TNFα is preferred, with certolizumab pegol as first line, and discontinuation of other biologics[27,34]. Among anti-TNFα drugs, for structural reasons, etanercept and certolizumab pegol can be administered until later in pregnancy: Etanercept until 30-32 weeks of gestation and throughout pregnancy for certolizumab pegol. However, continuation of treatment should be discussed individually with patients, considering all risks and benefits.

Recommendations for the use of anti-TNF therapy in the treatment of patients with rheumatologic diseases suggest continuing therapy safely until 30 weeks of pregnancy[35]. The most recent consensus statements from the Canadian Gastroenterological Association state that women at low risk of IBD relapse should stop anti-TNF therapy at 22-24 weeks, but, in all other cases, it is recommended that women with IBD receiving anti-TNF therapy continue treatment throughout pregnancy[36].

At present, infliximab, etanercept, adalimumab, certolizumab pegol, ustekinumab, and secukinumab are classified in FDA pregnancy category B, while no FDA category is assigned to newer biologics[27,28,37].

Hidradenitis suppurativa

HS is a chronic inflammatory dermatosis characterized by painful nodules and sinus tracts draining purulent material, typically located in the intertriginous areas. A population-based study in the United States found that the average annual incidence of HS was 12.1/100,000 women, more than double that of men (5.1/100,000)[38]. Furthermore, people aged 30-39 years had the highest incidence, followed by those aged 18-29 years, corresponding to women's childbearing years[38].

Hormones are thought to play a role in the pathogenesis of HS[38]. It has been suggested that increased progesterone levels during pregnancy may play a protective role in at least a subset of HS patients by promoting the differentiation of immunomodulatory Th2 and regulatory T-cells, while suppressing the release of pro-inflammatory Th1/Th17 cytokines. However, although about a quarter of women with HS may experience an improvement in their disease during pregnancy, the majority women with HS have a stable or worsening disease course[39]. In addition, more than half of women (60%) experience a postpartum disease flare (Table 1)[40].

In addition, childbirth also poses a challenge for patients with HS. A 2020 study found that up to 3.1% of patients with anogenital HS who delivered vaginally, HS interfered with delivery[41]. Of the patients who reported having a cesarean delivery, 33.9% reported poor incision healing and 51.2% reported the development of new inflammatory nodules over the cesarean scar[41].

Women with HS also have significantly lower odds (52%) of having a live birth compared to women without HS (70.74%)[42]. In addition, women with HS have been reported to be 2.51 times more likely to have an elective termination of pregnancy, as well as a higher risk of gestational hypertension and cesarean delivery, compared to healthy women[42]. Similarly, in a retrospective cohort study, pregnancies with HS were independently associated, after adjusting for maternal comorbidities, with increased risk of miscarriage, gestational diabetes mellitus, and cesarean section, compared to control pregnancies (Table 1)[43].

Regarding lactation, having HS lesions in the breasts can be a real obstacle. In fact, there are a limited number of options for pharmacological treatment of HS during lactation[38]. Deciding between treatment options for women with worsening HS during pregnancy or lactation requires an understanding of the efficacy and safety profile of drugs for both mother and fetus. In this document, we provide a review of the safety of commonly used drugs for HS. General recommendations are summarized in table 2.

Topical antiseptic washes: chlorhexidine and benzoyl peroxide

Topical antiseptic washes with antimicrobial activity may help reduce immune activation to resident skin bacteria in HS patients[44]. Chlorhexidine is considered FDA pregnancy category B; human data are lacking; however, animal studies have failed to demonstrate fetal harm and it is currently considered safe during pregnancy. On the other hand, topical application of chlorhexidine to the breast has not been shown to adversely affect infants[44].

Benzoyl peroxide wash is minimally absorbed through the skin and, if absorbed, is metabolized to benzoic acid, which is naturally found in certain foods. It is, therefore, considered safe during pregnancy[44].

Topical antibiotics: clindamycin, erythromycin, and metronidazole

Topical antibiotics may be considered for use in mild disease (Hurley Stage I and II). Topical clindamycin, erythromycin, and metronidazole are considered FDA pregnancy category B. When applied topically, they have very low systemic absorption, so the possibility of harm to the fetus is remote. These topicals are also considered compatible with breastfeeding, although further safety studies are needed[44].

Systemic antibiotics: clindamycin, metronidazole, rifampicin, moxifloxacin, and dapsone

Combination therapy with oral clindamycin (B) and rifampicin (C) is indicated for any stage of active disease and is considered first-line treatment in moderate-severe disease outside of pregnancy[44].

Systemic administration of clindamycin during the second and third trimester has not been associated with an increased frequency of congenital malformations. However, since there are no adequate studies during the first trimester, this agent should only be used if clearly needed. Clindamycin is excreted in small concentrations within breast milk and its use during lactation may have the potential to affect the infant's gastrointestinal flora, but it has generally been considered safe during breastfeeding by the American Academy of Pediatrics (AAPs)[44].

Rifampicin has been shown in rodent studies to be teratogenic at oral doses 15-25 times higher than the human dose[44]. In humans, a review including observational studies with more than 2000 exposures during pregnancy did not observe an excessive rate of congenital malformations[44]. However, rifampicin has been shown to cause postnatal hemorrhage in the mother and infant when administered during the past weeks of pregnancy. Prophylactic administration of vitamin K1 is, therefore, recommended to prevent this complication[44]. Rifampicin should only be considered if the potential benefits outweigh the risks to the mother and fetus. Although rifampicin is excreted into human breast milk, it is not known to cause adverse effects to nursing infants and is considered compatible during lactation[44].

The combination of rifampicin (C)-moxifloxacin (C)-metronidazole (B) has also demonstrated efficacy in the treatment of II and III Hurley stage recalcitrant HS[44].Although human data suggest a low risk of moxifloxacin use during pregnancy, studies have concluded that fluoroquinolones should be avoided due to possible fetal cartilage damage, as safer alternatives are generally available[44]. According to studies in rats, moxifloxacin may also be excreted in breast milk increasing the risk of arthropathy, although no human data are available. It is best to use caution and avoid moxifloxacin during pregnancy and lactation when possible[44].

Metronidazole has been shown to cross the placenta and rapidly enter the fetal circulation. However, overall, human data suggest a low risk of fetal harm[44]. Metronidazole is also secreted into breast milk at concentrations similar to plasma concentrations[44]. The AAP recommends discontinuing the medication 12-24 h before breastfeeding[45].

Dapsone (C) is a third-line agent for the treatment of Hurley Stage I or II disease[44]. There are no warnings of fetal abnormalities with use in any trimester; however, it can cause neonatal hyperbilirubinemia and dose-related hemolysis in the mother and infant[44]. Hemolysis may be important in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency, so initial measurement of G6PD levels should be performed. Dapsone is excreted in breast milk and dapsone-induced hemolytic

Table 2. Summary of guidance regarding medication use for hidradenitis suppurativa during pregnancy and breastfeeding[44]

Guidance	Pregnancy (FDA pregnancy category)	Breastfeeding (FDA pregnancy category)
Generally considered safe	Topical therapies: – Chlorhexidine (B) – Benzoyl peroxide – Clindamycin (B) – Erythromycin (B) – Metronidazole (B) Systemic therapies: – Clindamycin (B) – Metronidazole (B) – Metformin (B) – Zinc	Topical therapies: – Chlorhexidine (B) – Benzoyl peroxide – Clindamycin (B) – Erythromycin (B) – Metronidazole (B) Systemic therapies: – Clindamycin (B) – Rifampin (C) – Adalimumab (B) – Infliximab (B) – Metformin (B) – Zinc
Caution advised	Systemic therapies: – Rifampin (C) – Moxifloxacin (C) – Dapsone (C) – Adalimumab (B) – Infliximab (B) – Colchicine (C) – Apremilast (C) – Cyclosporine (C) – Corticosteroids (C)	Systemic therapies: – Metronidazole (discontinue 12-24 h before breastfeeding) (B) – Moxifloxacin (C) – Dapsone (C) – Colchicine (C) – Apremilast (C) – Corticosteroids (C) – Spironolactone (C)
Avoid	Systemic therapies: – Tetracyclines (D) – Acitretin (X) – Isotretinoin (X) – Finasteride (X) – Spironolactone (C) – Methotrexate (X)	Systemic therapies: – Cyclosporine (C) – Tetracyclines (D) – Acitretin (X) – Isotretinoin (X) – Finasteride (X) – Methotrexate (X)

FDA: Food and Drug Administration.

anemia has been reported in infants[45]. Caution is, therefore, advised with the use of dapsone during pregnancy and lactation.

Non-biologic immunomodulators: colchicine and apremilast

Colchicine (C) is known to cross the placenta. Animal studies have shown teratogenicity at concentrations within or above the therapeutic range. However, in a prospective observational cohort study of 238 colchicine-exposed pregnancies, it did not appear to be a major human teratogen or to have cytogenetic effects[46]. It is also excreted in breast milk, although limited data suggest that breastfed infants receive less than 10% of maternal dose[44]. However, colchicine may affect infant gastrointestinal system by influencing cell turnover and permeability[44]. Given these data, colchicine should be used with caution during pregnancy and breastfeeding[47].

Apremilast (C) has demonstrated efficacy in the treatment of patients with mild-to-moderate HS[44]. The incidence of teratogenicity and fetal loss in humans has not been established. However, exposure during organogenesis in monkeys revealed an increase in embryofetal death at doses 2.1 times the maximum recommended human therapeutic dose. Apremilast has been detected in lactating mice, but it is not known whether apremilast or its metabolites are present in human breast milk. Given the lack of data on the safety during pregnancy and lactation, caution should be exercised and this agent should only be used if the benefits clearly outweigh the risks[44].

Immunosuppressants: systemic corticosteroids and cyclosporine A

The potential effects caused by the use of SCS and CsA during pregnancy have been previously discussed in AD treatment section.

Biologic therapy: adalimumab, infliximab, ustekinumab, certolizumab pegol, secukinumab, and anakinra

Among anti-TNF-α agents, adalimumab, certolizumab, and infliximab have shown efficacy in the treatment of moderate-to-severe HS. On the other hand, ustekinumab and secukinumab and anakinra (IL-1 antagonist) have also been used in the treatment of HS with good results.

Recommendations for the use of anti-TNF-α drugs, ustekinumab, and secukinumab during pregnancy and lactation have been discussed previously (*see psoriasis*). Regarding the use of anakinra, although current evidence remains insufficient to establish recommendations for its use in pregnancy, a review of 40 pregnancies exposed to anakinra found no increase in the rate of miscarriage or congenital malformations in newborns[15].

Adjunct therapies: metformin and oral zinc

During pregnancy, metformin (B) can be considered as adjuvant therapy as it has not been shown to cause fetal adverse effects[44]. In general, metformin is considered compatible with breastfeeding, although there is a potential risk of hypoglycemia in infants[44].

Zinc supplementation has also demonstrated clinical efficacy in a small cohort of HS patients. Safety data during pregnancy are lacking; however, review studies investigating the use of up to 50 mg daily revealed no maternal or neonatal adverse effects[44].

Other treatments

Tetracyclines (D) have traditionally been used for the treatment of mild disease (I or II Hurley stage). This class of antibiotics has been associated with acute fatty liver of pregnancy when exposed in the third trimester. First trimester exposure has not shown an increased risk of congenital anomalies. Therefore, tetracycline use is contraindicated during late pregnancy[44]. Short-term use of tetracyclines may be considered during lactation; however, administration should be discontinued before 3 weeks of use to prevent dental staining. More research is needed on the use of tetracyclines during pregnancy and lactation, but they should generally be avoided[44].

Spironolactone (C) is beneficial as adjuvant or monotherapy in the treatment of HS. However, it leads to feminization of male fetuses and should be avoided during pregnancy. There is no evidence of adverse effects for infants with short-term exposure, but long-term data are lacking, so avoidance of use during lactation is currently recommended[44].

Other drugs used in the treatment of patients with HS, but totally contraindicated during pregnancy and lactation (category X) include: oral retinoids (acitetrine and isotretinoin), finasteride, and MTX.

Rheumatological IMIDs

Rheumatoid arthritis

The prevalence of RA in women of childbearing age is around 0.2%[48]. Pregnant women with RA have an approximately 1.5-2 times higher risk of hypertensive complications, fetal growth restriction, preterm delivery, and cesarean delivery. Venous thromboembolism occurs 2 to 4 times more frequently than in healthy pregnant women. Preterm delivery and growth restriction have been associated with disease activity and high-dose SCS treatment[48].

RA activity tends to be favorably affected by pregnancy. Improvement in disease activity has been reported in 48-60% of women with RA during pregnancy (Table 1). After delivery, 39-50% of women may experience a flare of the disease. Furthermore, conception should be planned at a time when the disease is fully controlled or its activity is minimal and, if possible, maintenance therapy compatible with both pregnancy and breastfeeding should be continued, especially due to the high risk of flares after delivery[48].

Systemic lupus erythematosus

The initial manifestation of systemic lupus erythematosus (SLE) occurs predominantly before the age of 30 years. The prevalence is estimated at 55/100,000 in the female population. The incidence of fetal, maternal, and obstetric complications is significant, including increased risk of preterm birth, growth restriction, pre-eclampsia, and thromboembolic disease, with disease activity being one of the most important risk factors[48]. The increased risk of preterm birth and pre-eclampsia arises from a combination of high clinical and serological activity, increasing in the case of positive antiphospholipid antibodies and lupus nephritis[48].

The likelihood of outbreaks is increased by 60% in pregnant patients compared to non-pregnant patients (Table 1). This risk depends on disease activity before conception, so pregnancy should be planned after

6-12 months of absence or mild disease activity. During the pre-conception phase, treatment should be reviewed and continued or switched to acceptable and safe immunosuppressive therapy during pregnancy to maintain remission. Hydroxychloroquine should always be initiated or continued if not contraindicated. Low-dose acetylsalicylic acid (ASA) is recommended for the prevention of pre-eclampsia in all patients[48].

Antiphospholipid syndrome develops in the setting of SLE in approximately 20% of cases. Antiphospholipid antibodies are associated with an increased risk of thrombosis and obstetric complications, especially late miscarriage and placental insufficiency. Depending on clinical and serological parameters, the treatment consists of ASA and/or heparin[48].

Gastroenterological IMIDs

Inflammatory bowel diseases

The prevalence of IBD, Crohn's disease, and ulcerative colitis is 300 and 400/100,000, respectively, with a peak incidence in the third/fourth decade of life[48].

Disease activity at the time of conception has the greatest effect on the course of the disease during pregnancy. Therefore, the current guidelines advise that conception should be planned during a remission period of at least 6 months[49]. Under these ideal conditions, about one-third of patients experience a flare during pregnancy (Table 1). On the other hand, active IBD at the time of conception is associated with preterm delivery, growth restriction, and an increased rate of the early miscarriage[50].

Clinical signs of increased disease activity are difficult to differentiate from symptoms that often develop during pregnancy, such as abdominal pain, nausea, rectal bleeding from hemorrhoids, and symptoms of anal stricture/constipation. Fecal calprotectin, unlike hemoglobin, C-reactive protein, and albumin, is not altered by pregnancy and, as such, appears to be adequate for predicting impending flares[48]. Gastrointestinal ultrasonography correlates well with fecal calprotectin and has a reliable negative predictive value; however, after 20 weeks of gestation, it is often not possible to adequately visualize the terminal ileum[48].

Patients with perianal involvement should receive proctological treatment in addition to primary, internal medical/gastroenterological, and obstetric/prenatal care. Regarding delivery, the European guidelines advise avoiding episiotomy, due to the risk of fistula formation[49]. Crohn's disease with perianal fistulas or proctitis is indications for elective cesarean section[49].

Conclusions

Close collaboration between dermatologists, rheumatologists, gastroenterologists, and obstetricians is needed to ensure adequate follow-up of pregnant patients with IMIDs. Large prospective registries of pregnant women may improve our understanding of the impact of IMIDs on pregnancy.

Finally, evidence-based consensus guidelines are urgently needed to assist in the appropriate management of these patients. The literature on the treatment of IMIDs during pregnancy and lactation is scarce, especially with regard to new biologics and small molecule therapies. Since interventional studies are not possible in this patient group, we emphasize the importance for specialists to publish any available cases.

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Conflicts of interest

None.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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REVIEW ARTICLE

Neoplasms in IMIDs: a review of the literature

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Abstract

Immune-mediated inflammatory diseases (IMIDs) are chronic and disabling diseases that share common inflammatory and immunological dysregulation. The association between IMIDs and the risk of cancer remains debatable. Inflammation is a double-edged sword for cancer as it can help destroy malignant cells but it can also promote the development of some cancers. The following review aims to provide a summary of the associations of neoplasms and the most common IMIDs and the possible relationship of the indirect risk caused by their chronic therapy. The risk of developing neoplasm is higher globally in patients with IMID, with different risk profiles and tumor types depending on the inflammatory pathology. Overall, lymphoproliferative disorders are the most common cancer in IMID patients. Nowadays, data available on the safety of the drugs used in IMID patients showed no increased risk of neoplasms in general, although more studies are needed.

Keywords: *Immune-mediated inflammatory disease. Neoplasms. Cancer. Tumor. Inflammation.*

Introduction

Immune-mediated inflammatory disease (IMID) is an actual concept for describing a group of chronic and disabling diseases that share common immunological and inflammatory pathways. Most frequent belonging diseases include psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis (RA), inflammatory bowel disease (IBD) – Crohn's disease (CD) and ulcerative colitis (UC) – and ankylosing spondylitis (AS).

Although each disease has its specific pathophysiology and epidemiology, the general prevalence of IMID is known to be about 5-7%[1]. Despite most IMIDs having a similar prevalence in both sexes, some of them have gender predominance like women in RA or men-predominance in SA. Furthermore, IMID patients had a higher risk of developing another IMID, with commonly known associations such as psoriasis and PsA or AR and IBD – with a relative risk (RR) of 7.63-8.62 in some studies[2].

Several studies in the last decades had associated IMID with a higher risk of other comorbidities in comparison to the general population with its consequent decrease in the health and quality of life (QoL), as well as the shorter life expectancy of these patients[3]. The positive association between these autoimmune diseases and increased risk of developing infections, cardiovascular and renal diseases had been recognized, as well as malignancies[4].

The risk of neoplasms in IMID patients might be increased direct and indirectly. First, the cytokine dysregulation and chronic inflammation of the disease itself it is thought to have a tumorigenic effect. Second, therapies for the control of IMIDs include mostly the decrease of the immune system using immunosuppressants, corticosteroids, and biological targeted therapy[5].

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Inflammation and malignancy

Although acute inflammation is beneficial and essential in normal circumstances, chronic inflammation is a well-known trigger for cancer and plays a main role in the molecular mechanisms of carcinogenesis. Indeed, inflammatory cells and mediators are present in most neoplasms, regardless of the location and causative agent[6]. In some neoplasms, inflammatory conditions are present before the malignant change increasing the cancer risk (as IBD and colonic cancer), while in other tumors, an oncogenic change will induce an inflammatory environment.

Inflammation in the tumor microenvironment is a feature of cancer and is known to be a key characteristic of carcinogens. Whereas the pathogenesis of carcinogenicity has been focused on external genotoxic activity, non-genotoxic mechanisms such as oxidative stress and inflammation promote mutation and DNA damage. In addition, carcinogens cause oxidative stress synergistically with inflammation, which fuels a vicious loop of cellular death, damage, and carcinogenesis[7].

Chronic pro-inflammatory activity promotes genetic and epigenetic aberrations in various pathways due to oxidative and nitrative damage[8]. Inflammatory cells are present in most neoplasms, promoting a correct microenvironment for the migration, invasion, and metastasis of malignant cells, and it is currently associated with bad prognosis[6,7].

In the early neoplastic process, malignant cells are powerful inflammatory activators due to the multiple antigenic and mutational differences. As the tumor progress, less immunogenic tumoral cells will escape to the immune system and progressively proliferate in oncological patients.

Under physiological conditions, the immune system initially promotes inflammatory responses to eliminate potential malignant cells. Normal inflammation is self-limiting, as the production of anti-inflammatory factors follows closely the pro-inflammatory ones. Failure of these mechanisms made persistence of the inflammatory response and the subsequent damage.

Unfortunately, there is another side of that coin, in which inflammation itself contributes directly to tumorigenesis. Tumor cells produce various mediators (such as cytokines, chemokines, and prostaglandins) of the inflammatory environment. One of the significant components of the leukocyte infiltrate of neoplastic tissues is tumor-associated macrophages (TAMs). Even if TAMs participate in killing neoplastic cells, they also promote tumoral growth by releasing angiogenic and lymphangiogenic growth factors that may potentiate tumoral progression[7,9]. However, closer studies will be needed on the relationship between TAM and oncogenic clinical importance, as it remains unclear.

IMID and risk of neoplasms

As we mentioned, IMIDs are characterized by chronic inflammation. Given the fine line between inflammation and cancer, it is not surprising that these immune-mediated diseases had a higher potential risk of developing some neoplasms. The following table 1 summarizes the most common association of tumors in the most prevalent IMIDs that we will develop in the following review.

RA

RA is a polygenic inflammatory autoimmune condition characterized by chronic joint inflammation and damage with secondary deformity and extra-articular damage. Management of RA consists of disease-modifying antirheumatic drugs (DMARDs) which change the natural course of the immunologic pathways. Prolonged immune dysregulation and inflammatory responses associated with RA increased cancer development risk according to literature.

The expected survival of RA patients is likely to decrease by 3-10 years according to the severity of the disease and the age of disease onset. It has been demonstrated that the excess mortality in persons with RA is largely attributable to cardiovascular disease (CVD). After CVD, cancer is the second most common cause of mortality in RA patients. In the reported meta-analysis, the risk of developing lymphoma – either Hodgkin or non-Hodgkin types – is significantly increased in RA patients (overall risk 2.08 1.80-2.39)[10]. Furthermore, lung cancer risk is slightly increased than in the general population (1.63 1.43-1.87)[10] probably due to chronic lung inflammation, presents even at early stages of RA. It has been suggested that interstitial lung disease in RA patients could increase the risk of lung cancer because many patients present parenchymal damage imaging findings at the diagnosis of cancer[11]. Other tumors such as breast, colorectal, prostate, cervix, and melanoma showed no differences compared to the general population[10].

Furthermore, the indirect risk of developing malignancies because of other aspects as lifestyle factors, smoking, or treatments must be specified. It is important to see any differences between patients treated with

Table 1. Overview of most frequent IMID associated with a higher risk of neoplasm

IMID	Neoplasm association
Rheumatoid arthritis	Hodgkin and non-Hodgkin lymphoma and lung cancer, related to the disease[9] NMSC increased risk due to DMARD therapy, in debate[11-14]
Psoriasis	NMSC, lymphoproliferative disease, lung and bladder neoplasms[16,17] Secondary to comorbidities possible higher risk of bladder, kidney, oropharynx, stomach, liver, gallbladder, and pancreas[17] Similar incidence of malignancies in patients with psoriatic arthritis[18,24]
Ankylosing spondylitis	Digestive and lymphoid hematopoietic neoplasms (multiple myeloma and lymphoma) are still up for discussion[24,25]
UC	Higher risk of colorectal cancer in UC than CD[27] Liver-biliary cancer and leukemia[29]
CD	Higher incidence of extra-intestinal neoplasms in CD than UC[29]. Upper gastrointestinal system, lung, urinary, bladder, lymphoma, biliary-liver cancer, and NMSC[29]

IMID: immune-mediated inflammatory disease, NMSC: non-melanoma skin cancer, DMARD: disease-modifying antirheumatic drugs, UC: ulcerative colitis, CD: Crohn's disease.

biological agents and DMARDs giving the chronic nature of the disease and the need for prolonged treatment. Some literature demonstrates that RA patients with prolonged doses of methotrexate and corticosteroids might also have an increased risk of non-melanoma skin cancer (NMSC)[12]. However, despite the immunomodulation of these therapies, the last studies showed no signal of increased risk for neoplasms in biologic and other therapeutic agents[13-15].

Treatment of RA in patients with cancer is complex. Given the lack of evidence for the use of specific therapies based on the risk of cancer, some published guidelines recommend that DMARDs should not be used in patients with active cancer and a recent diagnosis of RA, even if their use was considered safe[11,15]. For patients with a history of past cancer for at least 5 years, DMARDs can be used carefully. Some guidelines did not recommend the use of TNF inhibitors in patients with a history of cancer[11,13-15].

As for cancer treatments in patients with a known diagnosis of RA, it is common to discontinue the drugs for some time during the oncologic process. The consequences of the gaps in the RA treatment have not been clearly documented and there is no consensus for the management of the disease in patients with active cancer[11]. Conventional DMARDs should be used carefully in patients with active cancer if they are not receiving chemotherapy and if there are no interactions. These patients usually need specific and careful screening and monitoring as they are more susceptible to adverse reactions than patients without RA.

Psoriasis and psoriatic arthritis

Although we have pointed chronic inflammation as a major causal agent of carcinogenesis, this risk is more controversial in some inflammatory diseases as in psoriasis. Psoriasis is a chronic autoimmune inflammatory disease of the skin and joints. Some studies remark the importance of the macrophage phenotype, where M1 seems to have antitumoral activity – more active in psoriasis – meanwhile, M2 phenotype is more related to pro-tumoral environment – such as IBD and colorectal carcinoma[7]. The T helper 17, and to a lesser extent the T helper 1, mediated inflammatory response of psoriasis involves a huge number of neutrophils and monocytes in the skin that could destroy any emerging tumor cell[16].

The metabolic syndrome is an important driver of adverse cardiovascular outcomes and it has been proposed as an independent risk factor for developing myocardial infarction and neoplasia. Smoking, on the other hand, appears to have a role in the onset of psoriasis and increased risk of malignancies in this patient population[17]. The direct relation between neoplasm and psoriasis is still in debate. Baseline risk is difficult to assess due to usually chronic immunosuppressive treatments and higher rates of phototherapy and heliotherapy. Recent meta-analysis pointed out that patients with psoriasis appear to have a higher risk of keratinocyte cancer, lymphoproliferative diseases, lung, and bladder cancer[18]. Despite the data, cancer screening beyond the nationally recommended guidelines for age and sex is not required before initiating systemic therapy[17,18]. In subjects at increased risk for skin cancer, closer monitoring may be required. The highest association was keratinocyte

cancer, probably associated with the higher exposure to sunlight and more frequent follow-up of the patients with dermatologists than the general population.

When the association of developing tumors is compared between patients treated with biologic agents and conventional drugs, there is no association of higher risk[18-20]. Phototherapy with oral psoralen and ultraviolet A is directly and dose dependent related to increased risk of skin cancer but not for non-cutaneous malignancies[20,21]. No higher skin cancer was found with narrowband UVB and broadband phototherapies[22]. Treatment with methotrexate is related to a slightly increased risk of lymphoproliferative disorders according to some registers and also has been reported to be an independent risk factor for developing NMSC[20]. For cyclosporine A, there is an elevated risk of NMSC, especially when is associated with phototherapy[23].

As for psoriatic arthritis, 25% of patients with psoriasis will develop joint inflammation during the disease course and it is considered to be more severely affected. Malignancy rates in patients with PsA remain understudied. Even if the association of arthritis and cancer is still in debate, nowadays, investigations found similar prevalence and incidence rates of neoplasms compared with the general population[18,24].

AS

AS is an autoimmune disease that mainly affects the axial skeleton with male preponderance. Until now, the risk of neoplasms related to AS had not been fully clarified. Literature review and meta-analysis associated 14% increased risk of overall malignancy, with a specific higher risk of digestive and lymphoid hematopoietic neoplasms – principally multiple myeloma and lymphomas[25]. However, in recent studies, this increased specific risk was not significantly different from the general population when is adjusted for smoking and common comorbidities but AS patients had a 37% increased risk of mortality in the 5 years following cancer compared with patients without AS[26]. In summary, available data are still inconclusive but some clinical guides recommend tumor screening during the first 3 years of the diagnosis as the risk of neoplasia appears to be more frequent in the initial stages of the disease[27].

IBD

IBD is a chronic idiopathic inflammatory disorder of the gastrointestinal tract with possible systemic extension to joints, skin, and hepatobiliary system. The two main disorders include CD and UC. In patients with IBD, chronic inflammation is a major risk factor for the development of malignancies. It has been well demonstrated that patients with UC have an increased incidence of colitis-associated cancer (CAC) that correlates with the disease duration, activity, and location, as CD remains similar to the general population[28]. Bacterial invasion and chronic inflammatory response dysregulation are the main contributors of CAC with the subsequent inflammatory progression of hyperplasia, dysplasia, and carcinoma[29].

The risk of extra-intestinal cancer in patients with IBD remains uncertain, despite knowledge of a relatively high frequency of extra-intestinal manifestations among these patients. Some meta-analysis revealed that patients with CD were at an increased risk of extraintestinal cancer than UC, more specifically with higher rates of lung and urinary bladder (probably due to higher smoking rates), upper gastrointestinal system and NMSC, as well as potentially biliary liver cancer and lymphoma. On the other hand, UC patients were at an increased risk for liver-biliary cancer and leukemia, which was offset by a lower risk for lung cancer[30].

Patients with IBD have an increased risk of cancer from long-term intestinal inflammation and immunosuppressive treatments, especially classic immunosuppressive such as thiopurines or methotrexate. These medications promote direct DNA alterations and oncogene activation, and several studies have demonstrated an overall increased risk of cancer (RR 1.3-1.7)[31] with apparently no differences using TNF inhibitors[32].

Targeted therapies and cancer

Biologic agents have revolutionized the treatment of autoimmune diseases. The potential increased risk of malignancies due to the partial immune incompetence of these therapies is still controversial. Nowadays, experience with anti-TNF, anti-interleukin-1, or CD20 blockers like rituximab seems to be safe, with no clear risk of higher lymphomas or solid neoplasm[1,13].

Tumor necrosis factor inhibitors are commonly used in patients with IMID acting in the dysregulated immune system. TNF has been demonstrated to play a key role in the inflammation pathways and the ability to lyse tumors. The initial concern is that inhibition of TNF may also induce or increase the risk of malignancies, particularly lymphoma and skin cancers, including melanoma. However, despite anti-TNF therapy being often avoided in patients with a history of cancer, little is known about the risk of recurrence but, based on clinical trial data

and literature of observational studies or meta-analyses, showed no increased risk of recurrent or new primary cancer[15,33].

Rituximab is a monoclonal antibody against the protein CD20 approved for refractory RA. The latest researches on this drug seem to point rituximab as a safe and effective medication, and the most common concerning side effects include reactivation or development of infections, failure of immunization, and paradoxical reactions[34]. For the moment, the use of rituximab in the treatment of IMIDs has not been associated with a long-term increased risk of malignancies[35].

JAK inhibitors such as tofacitinib and baricitinib have also revealed a safe profile in long-term security in controlled trials with slightly more risk of some infections such as opportunistic infections and viral infections as herpes zoster, but no greater number of neoplasms[36,37]. Despite the available data, long-term follow-up and further studies are needed.

As for IL-17 inhibitors, recently, it has been suggested the role of IL-17 in cancer surveillance with pro- and/or anti-tumorigenic function depending on the context[38]. Nowadays, according to prospective studies from clinical trials about observed versus expected number of malignancies, no higher significant risk in patients treated with anti IL17 has been demostrated[39-41]. Despite the given information, long-term safety data from patient registries are still needed to provide a complete overview of cancer risk.

However, the interpretation of the data should have some considerations. First, the selection of patients therapy usually is correlated with its severity, as patients initiating biologic therapy usually had more active disease than those treated with other immunosuppressive agents. Second, therapy switching is common in real practice which makes it difficult to differentiate de exposure of the different drugs. In addition, many patients treated with biologic therapy had been previously treated with other drugs.

Conclusion

It seems that the diversity and plasticity of chronic inflammation and the dual potential of cancer-related inflammation (pro-tumoral vs. antitumoral activity) are the two faces of the same coin, with different inflammatory cell phenotypes. The exact mechanism of "good" immune responses is not clear yet but promoting cancer-inhibiting inflammatory responses with low cancer-promoting inflammatory response might be the clue for useful approaches in the prevention, diagnosis, and treatment of cancer. It has been well demonstrated that some IMIDs had an increased risk of cancer when compared with the general population. RA has a strong relation with higher rates of lymphoma and lung cancer. Psoriasis patients are more likely to have NMSC and an indirect higher risk of neoplasms due to comorbidities such as alcohol and smoking. In subjects at increased risk for skin cancer, closer monitoring may be required. As for IBD patients, a higher risk of colorectal cancer is more associated with CD than in UC.

The therapeutic aims for IMIDs include the control of chronic inflammation, prevention of tissue damage and comorbidities, and improvement of QoL and long-term remission. The risk of new recurrent systemic malignancies is similar between biologics and non-biologic treatments and they are generally considered safe. Conventional therapy with MTX and CsA had a higher risk of NMSC, especially when they are used associated with phototherapy or other treatments.

Given the complexities in the clinical management of patients with IMID and cancer, a multidisciplinary approach is always preferable to enhance patient welfare. Therapeutic choices should be consensual with the patient assuring a balance between QoL and survival.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

Autologous hematopoietic stem cell transplantation for refractory Crohn's disease

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Abstract

Despite recent advances in Crohn's disease (CD) therapy, with ever-new treatments available, there is still a relevant percentage of patients with refractory disease who do not achieve adequate clinical response and are not amenable to intestinal surgery. A joint consensus of the European societies for blood and marrow transplantation and inflammatory bowel disease has recognized the therapeutic role of autologous hematopoietic stem cell (HSCs) transplantation in this cluster of patients. The therapy produces a reset of patients' immune system and the subsequent recovery of more self-tolerant inflammatory cells. In several case series and prospective clinical trials, this treatment was demonstrated to be able to induce clinical remission and heal mucosal damage, although providing only a temporary improvement. The use of deep immunosuppression as part of transplanting protocols represents the major limitation of this technique as causes a high adverse event rate, including mortality of up to 2%. Many new protocols have been assessed and are under investigation with the intent to reduce complications. The present review summarizes evidence of the efficacy and safety of autologous HSCs transplantation in refractory CD.

Keywords: *Transplant. Crohn. Refractory. Hematopoietic.*

Introduction

Since the first description of Crohn's disease (CD) in 1932 many advances have been achieved toward the control of clinical symptoms and the improvement of patients' quality of life; however, there is still no cure for the disease[1]. CD has now become a global disease with an increased incidence in newly industrialized countries and with a stable incidence in Western countries[2]. Being a multifactorial disease involving genetic susceptibility, environmental factors and intestinal microbiota, current therapeutic strategies, targeting one or few potential causes of the disease, only ensure a temporary control and improvement but not a definite solution.

Not all patients with CD show the same disease course, with the majority of cases with mild or well-controlled disease and a relevant percentage of patients with a severe course that requires several changes in therapeutic strategies, including surgery[3].

Medical therapies have changed significantly over the years, currently including steroids, immunosuppressive drugs and multiple biologic agents; moreover, new drug classes have been developed and are under investigation[4]. However, up to 30% of CD patients do not achieve clinical remission despite currently available treatments[3]. This cluster of patients represents a challenge for gastroenterologists and obliges them to explore the use of limited evidence immunomodulators, dietary strategies, and participation in clinical trials or invasive surgeries.

Refractory Crohn's disease

In 2021, an international consensus from the European Crohn's and Colitis Organization defined the

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characteristics of refractory inflammatory bowel disease (IBD)[5]. Refractory CD refers to patients who do not achieve adequate response despite the use of all available medical therapies (primary and/or secondary failure) and may not be amenable to intestinal surgery due to extensive intestinal disease, at risk for short bowel syndrome, previous multiple surgeries and, in some cases, the unwillingness of the patient to accept a permanent ostomy. There are no direct predictors of refractoriness; however, a more severe course of the disease is usually associated with age at onset < 40 years, perianal disease, upper gastrointestinal, and ileocolonic location[6,7].

The availability of medical therapies changes over time with new molecules possibly available in the next future, such as Janus kinase 1 inhibitors, sphingosine 1-phosphate receptor modulators (ozanimod), or the possibility to combine treatments (dual therapy)[8]. Thus, the definition of refractory CD is variable and evolving and must be carefully applied according to patients' medical history figure 1.

Hematopoietic stem cell (HSCs) transplantation

HSCs are characterized by the ability to self-renew and differentiate into all mature blood lineages[9,10]. This process is regulated by a complex network of stromal interactions with soluble and cell-bound cytokines[11]. The therapy of HSC transplantation allows to reset patient's immune system (lymphoablation) and restarts it with the generation of new self-tolerant immune cells, thus permitting a temporary remission of the disease. The most common technique of HSC transplantation adopted in CD is based on peripheral blood cell collection. After the recipient's bone marrow ablation (conditioning), the migration and "homing" of intravenously transplanted stem cells to the hematopoietic microenvironment in the bone marrow niches of the recipient allows the reconstitution of the cell pool[12].

The transplant may be allogeneic, syngeneic, and autologous, depending on the donor's availability and indications for transplantation. The most common indications for allogeneic HSCT are hematological malignancies and premalignant conditions[13]. Syngeneic or allogeneic HSCTs are also used for acquired disorders of marrow function (i.e., aplastic anemia) and correction of congenital hematopoietic or immunological defects (i.e., thalassemia and immunodeficiency syndromes)[14,15]. In refractory CD, autologous HSCT is considered the safest option[16].

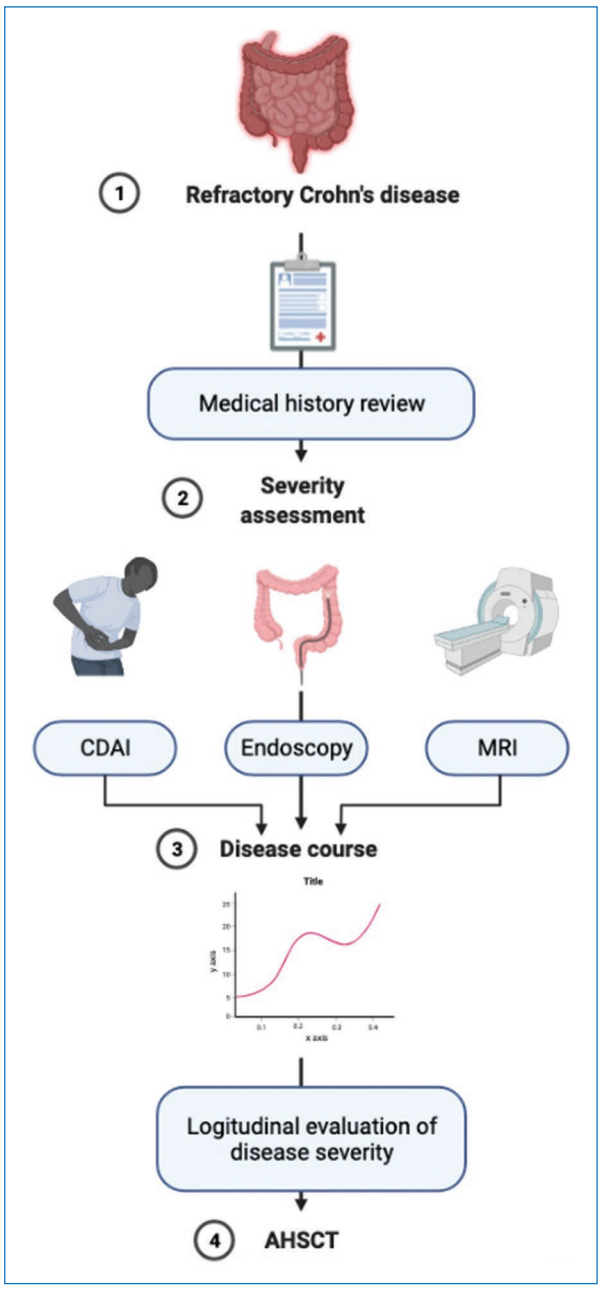

Figure 1. Eligibility assessment for autologous HSCT. CDAI: Crohn's disease activity index, MRI: magnetic resonance imaging, AHSCT: autologous hematopoietic stem cell transplantation.

Autologous HSCs transplantation in CD

Eligible candidates and screening

Potential candidates are strictly selected by a review of their medical history to confirm refractoriness to correctly and adequately administered therapies. Patients must show a severe disease activity, evaluated according to

Table 1. Standard protocol for autologous HSCT in Crohn's disease

Screening	– Confirm eligibility (refractory Crohn's disease) – Exclude severe comorbidities, pregnancy – Cardio-respiratory function assessment, bone marrow aspiration, DEXA scan, exclude latent infections, fertility preservation
Mobilization and harvesting	– Hospital admission – Safety protocols – Cy 2g/m^2/day (2 days) + G-CSF 10 mcg/Kg/day (after 5 days) – Minimum recollection 3 × 10^6 CD34+ /Kg
Conditioning and transplant	– Hospital admission – Safety protocols – Cy 200 mg/kg + rATG 7.5 mg/kg (+ CCS) – CD34+ cells reinfusion – Engraftment if neutrophils > 0.5 × 10^9/L and platelets > 20 × 10^9/L (at least for 3 consecutive days)
Follow-up	– Hematological and gastroenterological follow–up during at least 1 year

DEXA: dual-energy X-ray absorptiometry, CY: cyclophosphamide, rATG: rabbit anti-thymocyte globulins, CCS: corticosteroids.

clinical scores such as crohn disease activity index (CDAI), endoscopic exploration, and radiology (entero- Magnetic resonance imaging). Moreover, a longitudinal evaluation of severe disease course is necessary to identify eligible patients. No concomitant medications are allowed, except for steroids. Thiopurines must be suspended 2 weeks before, biologics 4 weeks before transplant.

Patients considered eligible for autologous HSCT must pass a full medical assessment, including bone marrow aspirate, left ventricle ejection fraction, pulmonary function test, dental evaluation, and bone densitometry (DEXA scan). Potential latent infections must be ruled out: cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus, Epstein-Barr virus (EBV), human T-lymphotropic virus Type 1 and 2, hepatitis viruses, human immunodeficiency virus, Toxoplasma gondii, and tuberculosis. Fertility preservation is highly recommended. Patients with severe comorbidities, poor compliance, or pregnant women are excluded from transplantation. The protocol is summarized in table 1.

Mobilization and harvesting

Mobilization has the objective to release HSCs (CD34+ cells) into the blood torrent. The most common protocol is based on the combination of a priming agent, intravenous cyclophosphamide (Cy) 2 g/m^2/day on 2 consecutive days, and subcutaneous granulocyte colony-stimulating factor (G-CSF) 10 mcg/kg/day after 5 days from last Cy infusion until leukapheresis is completed[17,18]. This regimen requires patient hospitalization in a safe setting with the use of antibiotic prophylaxis and, in some cases, parenteral nutrition, due to the high risk of infectious complications. For leukapheresis (harvesting), the minimum requirement of CD34+ cells mobilized and extracted is 3 × 10^6 CD34+/kg and, whether possible, at least 2 × 10^6 CD34+/kg cells for emergency use. In most protocols unselected CD34 + cells are used, since no clear benefits have been described with CD34+ cell-enriched or selected transplants[19]. HSCs are cryopreserved in dimethyl sulfoxide 10% until transplantation.

Recently, a new mobilization protocol, which avoids using Cy as a priming agent to minimize adverse events, has been presented. It is based on the use of G-CSF 12–16 g/kg/day up to 5 days and the optional injection of plerixafor (AMD 3100) 240 g/day in case of inadequate mobilization; this protocol does not require patient hospitalization during mobilization[20].

Conditioning and transplantation

A nonmyeloablative conditioning regimen is generally administered with a total dose of 200 mg/kg of Cy and 7.5 mg/kg of rabbit anti-thymocyte globulin (ATG); 500 mg of corticosteroids are added for 3 days to reduce adverse effects of rabbit ATG. Harvested HSCs are finally infused and engraftment is confirmed by hematologic recovery when the absolute neutrophil count is > 0.5 × 10^{9}L and platelet count > 20 × 10^9/L for at least 3 consecutive days.

Recently, an alternative protocol has been presented as part of a multicenter observational study (ASTIC lite): patients were mobilized with low-dose Cy (1 g/m^2) and G-CSF, whereas conditioning was based on fludarabine (125 mg/m^2), Cy (120 mg/kg) and rabbit ATG

(7.5 mg/Kg); however, the study was suspended due to safety concerns.

During conditioning and transplantation, it is extremely important to offer supportive care, including hospitalization in isolated rooms equipped with high-efficiency particle arresting (HEPA) filters and antimicrobial prophylaxis, targeting the most common bacteria, *Pneumocystis jiroveci* and HSV; prophylaxis is maintained until immune system recovery. A low microbial diet is adopted until CD4 recovery (> 400/mm^3) and antifungal prophylaxis until neutrophil recovery (> 500/mm^3). Patients may need irradiated transfusions of red cells or platelets and only in case of prolonged neutropenia, the use of G-CSF. During the aplasia period, parenteral nutrition is required. Patients are followed-up by both hematologists and gastroenterologists during the 1st year[21].

Efficacy

The concept and application of HSCT as primary treatment in immune-mediated inflammatory diseases (IMIDs) started at the end of the '90s and for decades it was supported by experiments on animals or by unexpected healing of IMIDs observed in patients treated due to hematological or oncological diseases. In 1997, the European group for Blood and Marrow Transplantation (EBMT) defined guidelines on indications, contraindications, and protocols of HSCT in autoimmune diseases, moreover, they created a database to collect clinical data and monitor the efficacy, toxicity, and viability of different protocols of transplantation[22].

In the IBD field, autologous HSCT was applied almost exclusively in CD and many single case reports or case series were described until the publication of the "Autologous Stem Cell Transplantation International Crohn's Disease" (ASTIC) prospective study in 2015. See Table 2.

In 2005, the University of Chicago published the first evidence of the efficacy of autologous HSCT in treating 12 patients with refractory CD and described a remission rate of 91.6%[23]. The authors observed symptomatic improvement in the majority of patients after mobilization of hematopoietic progenitors; however, it was attributed to the immunomodulatory effects of drugs used in this phase (Cy). Later, in 2010 the same group published a phase I study with a 5-year follow-up in 24 patients, including 12 patients from the previous study, to evaluate the safety and efficacy of autologous HSCT in patients with severe CD refractory to anti-TNF therapy[24]. HSCs were mobilized with Cy 2 g/m^2 and G-CSF 10 μg/kg/day, *enriched ex vivo* by selecting CD34+ cells and re-infused after conditioning with Cy 200 mg/kg and horse ATG 90mg/kg or rabbit ATG 6 mg/kg. Eighteen patients out of 24 were followed up for 5 years after transplanting. In the short-term, all patients entered remission (CDAI < 150). The percentage of patients free from CD therapy after transplant was 91% at 1 year, 63% at 2 years, 57% at 3 years, 39% at 4 years, and 19% at 5 years. The percentage of patients in remission (CDAI < 150), free from steroids and free from medications at any time interval after transplanting was 70%, 80%, and 60%, respectively.

In 2008, an Italian series of four patients was published: no CD34+ cells selection was performed but the results were comparable to previous studies. After 3 months, all patients achieved clinical remission, whereas endoscopic remission was achieved by two out of four patients[19]. Interestingly, the authors observed a worsening in the clinical conditions of patients during and after mobilization. A German case series including 12 patients described a conditioning regimen with high-dose Cy, without the use of ATG: 7 out of 9 patients showed an early relapse during follow-up, and this was partially explained by eliminating ATG from the conditioning regimen[25]. ATG is composed of purified gamma globulins containing primarily IgG against T cells and reduces the chance of relapse by contributing to the elimination of autoimmune cells[26].

In 2015, the first clinical trial of autologous HSCT for refractory CD (ASTIC) was conducted to confirm the efficacy of transplantation and assess the role of immunosuppression with Cy[17].

The ASTIC study compared the clinical benefits of mobilization of HSCs followed by conditioning and transplant (group of early transplanting) versus mobilization only followed by ordinary clinical practice; this last group could be rescued with autologous HSCT in case of persistent symptoms after 1 year from mobilization (group of late transplanting). The primary endpoint was the combined medication-free clinical and endoscopic remission at 1 year from transplant and was achieved only by 2 patients in the early transplanting group. However, in comparison with the mobilization-only arm, a secondary analysis showed that more patients in the transplanted group could stop the immunosuppressive therapy (35.3% at 3 months) and more patients in the transplanted group were in clinical and endoscopic/radiologic remission at 1 year of follow-up[27]. These results supported the concept of the beneficial effects of transplanting and not of mobilization, moreover, in line with subsequent observations, the study

Table 2. Clinical studies on autologous HSCT in Crohn's disease

Authors	Year (study design)	Transplanted patients	Harvesting	Remission rate (patients)	Relapse rate/ follow-up	Mortality rate (patients)
Oyama et al.	2005 (Phase I clinical study)	12 pts	Enriched CD34+	91.6% (11/12)	16.7%/18 months	0
Cassinotti et al.	2008 (Prospective study)	4 pts	Unselected CD34+	100% (4/4)	25%/16.5 months	0
Burt et al.	2010 (Phase I-II clinical study)	24 pts	Selected CD34+	100% (24/24)	9%/1 year 43%/3 years 81%/5 years	5% (1)
Clerici et al.	2011 (Phase I-II clinical study)	6 pts	Unselected CD34+	100% (6/6)	16.7%/1 year	0
Hasselblatt et al.	2012 (Phase I-II clinical trial)	9 pts	Selected CD34+	55.5% (5/9)	77.8%/3.1 years	0
Snowden et al.	2014 (Retrospective study)	6 pts	Unselected CD34+	83.3% (5/6)	NA	0
Hawkey et al.[17]	2015 (Multicenter prospective clinical trial)	23 pts	Unselected CD34+	8.7% (2/23) Sustained remission	NA 56.8%/1 year	4.3% (1)
Lindsay et al.[27]	2017 (Retrospective analysis)	40 pts		38.5% (15/39)		2.2% (1)
Ruiz et al.[36]	2017 (Prospective study)	14 pts	Unselected CD34+	92.9% (13/14)	NA	0
Jauregui -Amezaga et al.[21]	2016 (Safety study)	26 pts	Unselected CD34+	NA 70% (20/29)	NA 39%/1 year 48%/2 years 53%/3 years 85%/5 years	5% (1)
Lopez-Garcia et al.[18]	2017 (Single-center prospective study)	29 pts				3.4% (1)

CD: cluster of differentiation, NA: not applicable.

suggested that sustained clinical remission after autologous HSCT was not probably determined by the administration of Cy and G-CSF[28,29].

The largest case series, with 29 refractory CD patients treated with autologous HSCT at a single center, was described by the group of Barcelona[18]. Patient population showed refractoriness to corticosteroids, thiopurines, methotrexate, and anti-TNF agents. Patients passed a rigorous eligibility assessment and were hospitalized during mobilization (mean hospitalization time of 22 days) with the intent to maximize procedure safety. A standard mobilization regimen was used (Cy + G-CSF). HSCs were collected from peripheral blood by apheresis. The conditioning regimen consisted of Cy + rabbit ATG and, during the past 3 days, high-dose steroids (500 mg daily). In addition to the security measures applied during mobilization, both conditioning and transplanting included patient isolation in special rooms with high rendering filters (HEPA), prophylactic antibacterial and antifungal treatment, and prophylaxis for HSV (in patients with positive serology) and *P. jirovecii*. The transfusion of irradiated red blood cells or platelets was administered according to standard practice. Parenteral nutrition was administered during the period of aplasia. At 6 months from transplant, 70% of patients showed medication-free clinical remission (CDAI < 150). The proportion of patients in medication-free clinical and endoscopic remission (CDAI < 150, SES-CD < 7) was 61% at 1 year, 52% at 2 years, 47% at 3 years, and 15% at 5 years. Patients who relapsed during follow-up were retreated with biologics (anti-TNF with or without immunosuppressive drugs), recovering clinical remission in 80% of cases.

In 2018, a survey from the EBMT registry defined an overall 68% rate of remission or significant symptomatic improvement in patients with refractory CD with a median follow-up of 41 months, moreover, in those patients who had reinitiated a medical therapy, 57%

could achieve again clinical remission or significant improvement[16].

These data suggest that autologous HSCT does not represent a "cure" for CD; however, it can change the disease's natural history and permit to recover response to medications that patients were refractory to.

Finally, still little is known about predictors of response to autologous HSCT. According to the previous studies, colonic location and inflammatory phenotype with endoscopic lesions were associated with a better response to treatment, whereas structuring and penetrating phenotypes showed no benefit from transplanting[17,18].

Safety

The major complications of HSCT are septic and related to the use of high chemotherapy doses; moreover, drug toxicity and prolonged immunodeficiency cause an extended recovery process[30]. Adverse events can be controlled by the design of risk-specific supportive care regimens that reduce the incidence of transplantation morbidity and mortality[21].

Normally HSCT-related complications are broadly classified into infections, early non-infectious complications (within 3 months from HSCT), late non-infectious complications (after 3 months from HSCT) and graft-versus-host disease, which may require prolonged immunosuppressive therapy. In autologous HSCT the engraftment is rapid (7-14 days), thus the incidence of infections is lower than in allogeneic transplants and graft-versus-host disease is rare.

The EBMT registry described a high complication rate, mainly infections, for autologous HSCT in IMIDs and a mortality rate of up to 11%, depending on the protocol used and the disease treated, being higher in systemic diseases and lower in localized ones[31]. Mortality from autologous HSCT in IMIDs is associated with the grade of experience of the medical center as a higher number of transplants means a more rigorous selection of candidates and better management of possible complications[32]. In the case of CD mortality accounts for up to 2%[33].

In the last decades, the safety of HSCT has increased notably, due to the reduction of the intensity of conditioning regimens, the use of peripheral blood stem cells and the improvement of measures to support and select patients. In the Barcelona cohort, one patient died due to a systemic infection for CMV despite early antiviral therapy 2 months after transplantation and one patient required colectomy for a CMV and EBV co-infection. In the first transplanted patients, severe infections were observed during mobilization and conditioning phases, including bacteremia and septic shock, consequently, several measures to increase safety were adopted. The change in prophylactic antibiotic therapy, the use of a food safety-based diet and parenteral nutrition during the periods of aplasia achieved a reduction in the incidence of severe infectious events[21]. Moreover, smoking and perianal disease were identified as risk factors for adverse events[18].

Among new strategies to reduce complications, less aggressive chemotherapy regimens during mobilization and conditioning phases have been evaluated. For two decades Cy has been the standard treatment in mobilization regimens. Its use at high doses causes the liberation of proteases and the cleavage of adhesion molecules (VCAM-1 and CXCR4) culminating in the release of HSCs into the peripheral blood, although with significant cytotoxicity causing numerous side effects[34]. Moreover, whilst in many cases of HSCT for malign hematologic diseases the use of Cy is endorsed for its therapeutic role on the disease, in the case of CD, there is no need for a cytotoxic effect during mobilization[27]. Recently, with the intent to reduce the impact of chemotherapies on autologous HSCT, a Cy-free mobilization regimen has been proposed. It is based on the use of G-CSF alone, which was demonstrated to mobilize HSCs in up to 70-80% of treated patients[35]. In case of mobilization failure (< 20.000 CD34+/kg) after 7 doses of G-CSF, a rescue strategy is applied using subcutaneous plerixafor. Preliminary data suggest a better safety profile of this protocol, which allows to perform mobilization in the outpatient setting[20].

Conclusion

Refractory CD still represents a challenge for IBD specialists as there are no clear predictors to identify the disease course and therapies are insufficient in this group of patients. Autologous HSCT is a rescue therapy as it eliminates the self-reactive lymphocytes with different regimes of immunosuppression and restores a normal immunological tolerance. However, acting only on one of the mechanisms of disease pathogenesis, HSCT may not be considered a cure but rather an alternative therapeutic strategy. It may stop or slow disease progression and achieve prolonged periods of remission, thus modifying the disease's natural history without the need for chronic maintenance with steroids or immunosuppressive drugs and their related side effects. Safety is the major concern of this therapy due to the high rate of septic adverse events. Future efforts

are directed toward reducing complications and improving efficacy together with identifying predictors of response.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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REVIEW ARTICLE

Advances in the surgical treatment of Crohn's disease

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Abstract

Despite the advances in medical treatment of Crohn's disease (CD), most of the patients require one or more surgical bowel resections during their life for complicated disease. Surgery for CD has gone through progressive technical refinement over time. Minimally invasive surgery and bowel-sparing techniques have been validated with regard to surgical trauma reduction, and their role has been clearly defined in the current guidelines. Nevertheless, continuous technology advancement has further expanded the surgical tools with single-access and robotic-assisted surgery. With the aim of further reducing the impact of surgery, the concept of "strategic surgery" has been explored. On the one hand, patients' optimization before surgery has the potential to reduce post-operative complications. On the other, early intervention for the uncomplicated disease before medical therapy escalation has been demonstrated equally reliable with respect to biologics in terms of quality of life and advantageous in terms of health-care costs. Ultimately, a better comprehension of the pathological mechanisms underlying the disease is the key to radically changing the surgical management of both abdominal and perianal CDs. In fact, novel surgical strategies aiming at reducing disease recurrence which take into account the anastomotic configuration and the role of the mesentery as an active player in the disease process have been pursued in the past decade. The purpose of this review is to describe the recent innovations in the surgical treatment of CD focusing on their potential impact on the short- and long-term outcomes.

Keywords: *Crohn's disease. Perianal Crohn's disease. Colorectal surgery.*

Introduction

Crohn's disease (CD) is a chronic inflammatory disease with a prevalence of 300 per 100,000 persons[1] in the Western countries, characterized by skipping intestinal lesions interspersed with the normal mucosa, which may affect all the gastro-intestinal tract and, in particular, the terminal ileum, with possible formation of strictures, fistulae, and abscesses[2].

In the past years, the increasing use of biological and immunomodulating treatments has changed medical management of CD, significantly decreasing and delaying the need for surgery[3]. However, up to 80% of CD patients still require surgical intervention at least once in their life. Surgery is indicated to treat CD complications (stricture, fistulas, and abscess), but is not curative. In fact, post-operative CD recurrence is common and usually occurs at the anastomotic site, often leading to further surgical treatment[4].

Perianal fistulizing CD (PFCD) is a common manifestation of CD and it is associated with severe and disabling symptoms that significantly reduce patients' quality of life. Medical therapy combined with surgical management is the current approach to PFCD and provides an adequate healing rate[5].

In the past decades, several efforts have been made to improve the surgical approach to CD, minimally invasive surgery and bowel-sparing techniques have been validated concerning surgical trauma reduction, and their role has been clearly defined in the current guidelines.

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Nevertheless, continuous technology advancement has further expanded the surgical tools with single-access and robotic-assisted surgery.

To further reduce the impact of surgery, the concept of "strategic surgery" has been explored. On the one hand, patients' optimization before surgery has the potential to reduce postoperative complications. On the other, early intervention for uncomplicated disease before medical therapy escalation has been demonstrated equally reliable with respect to biologics in terms of quality of life and advantageous in terms of health-care costs. Ultimately, a better comprehension of the pathological mechanisms underlying the disease is the key to radically changing the surgical management of both abdominal and perianal CDs. In fact, novel surgical strategies aiming at reducing disease recurrence which take into account the role of the mesentery as an active player in the disease process have been pursued in the past decade.

The purpose of this review is to describe the recent innovations in the surgical treatment of CD for ileocolic and perianal disease focusing on their potential impact on the short- and long-term outcomes.

Upper gastrointestinal (UGI) CD

CD of the UGI tract is referred to esophagus, stomach, duodenum, and jejunum involvement. Typically, the lesions are aphthae, erosions/ulcers, fistulas, and strictures that could be diagnosed during endoscopic evaluation. Lesions' rate of UGI tract has been reported with great range variation (6.5-75%). However, only a small number of patients with endoscopically detected UGI-CD have symptoms[6]. Esophageal CD has an incidence of 6.5% in pediatric patients, while it is less common in adults (approximately 1%). Mild and distal part of the esophagus are the sites where lesions most frequently occur. Endoscopic dilatation is an effective treatment with a high rate of short-term outcomes and low rate of complications in case of gastroduodenal strictures, this procedure allows a redilatation for relapse[7]. Gastroduodenal CD is a rare site of disease with a total rate of 1-4% of patients[8]. Surgery should be performed in case of dysplasia or cancer or complicated disease (symptomatic fistulas or stenosis). However, surgical techniques are not well established due to the lack of data in the literature. ECCO guidelines[9] consider effective options: partial gastric resection, strictureplasty, and Roux-en-Y bypass in case of gastric antrum or duodenal bulb involvement, avoiding routine vagotomy. The second and third part of duodenum could be treated with strictureplasty, while more demolitive interventions are only indicated as a last resort[9].

Ileal and ileocolic CD

Nearly 80% of ileocolic CD patients require a surgical resection within 10 years from the diagnosis[6]. In the past decades, several efforts have been made to improve the surgical management of ileocolic CD patients, with the main purpose of reducing the impact of surgical trauma, the rate of post-operative complications, ameliorating post-operative outcomes, and shortening the length of hospital stay.

Predominantly inflammatory or predominantly fibrotic strictures: surgical strategies

Inflammatory strictures could be treated with medical therapy or surgery. Usually, surgical management is reserved for patients who do not respond to drug therapy.

The LIR!C trial proved laparoscopic ileocecal resection in patients with non-structuring ileocecal CD as a cost-effective treatment with similar results in quality of life when compared with infliximab therapy[10]. The long-term follow-up of LIR!C trial showed a high rate (74%) of patients who did not need additional biological treatment in the resection group, while half of the patients in the infliximab group had an ileocecal resection after a median follow-up time of 5 years[11]. Time of surgery could modify the post-operative course in CD. Early surgery in ileocecal CD reduces the risk of clinical recurrence and the rate of patients who need anti-TNF therapy when compared with patients that receive a late surgery, nevertheless, the likelihood of reoperation is not related to the time of surgery[12].

In predominantly fibrotic CD strictures, the likelihood of a good response to medical treatment is poor. Therefore, surgical resection or strictureplasty is required in these cases. The need for reducing postoperative complications and improving functional outcomes led to reconsider the use of extended bowel resections in CD. Indeed, extensive resection in CD is considered unnecessary because the recurrence rate is similar in patients treated with a wide resection compared with those underwent limited intestinal resection[13]. Therefore, ileocecal resection is usually preferred for limited small bowel disease, strictureplasty is recommended in case of multiple strictures, previous significant small bowel resection (> 100 cm), small bowel syndrome, or recurrent ileocolic anastomotic strictures[14]. Conventional

strictureplasty – Heineke-Mikulicz and Finney – may not be feasible in patients with multiple strictures in a short length of bowel or with a structure longer than 30 cm. Concern about Finney strictureplasty is related to the creation of a large non-functional diverticulum, resulting in bacterial overgrowth. While intestinal absorptive function is preserved in Heineke-Mikulicz strictureplasty, indeed patients rarely developed metabolic dysfunctions after this procedure[15]. In case of long strictures (more than 20 cm), the Michelassi strictureplasty – consisting in dividing the bowel in the middle part of the stricture and restoring the intestinal continuity with a side-to-side isoperistaltic strictureplasty, can be applied[16]. Long-term results showed that Michelassi strictureplasty is a safe, effective, and durable intestinal sparing procedure with a high range of patients which not developed recurrences after surgery[17]. A modified side-to-side isoperistaltic strictureplasty over the ileocecal valve was introduced in case of bowel length disease more than 20 cm which includes the ileocecal valve[18]. This technique is an alternative procedure to the ileocecal resection in extensive terminal ileitis in CD and it avoids the incorporation of healthy bowel length in the long strictureplasty. However, it is contraindicated in case of any septic complications, extensive fibrotic bowel wall, or mesenteric thickness. The authors reported post-operative ileus as a common complication related to this type of surgery, nevertheless, an endoscopic mucosal improvement was observed in 44.7% of patients at 6 months after surgery[19].

Intra-abdominal fistulas and abscesses in CD

Intra-abdominal fistulas occurred in approximately 30% of CD patients and they are classified by indicating the bowel segment where they originate and followed by the non-diseased target organ (i.e., enteroenteric, enterocutaneus, enterosigmoid, and enterovescical)[20]. Usually, magnetic resonance imaging (MRI) is the most useful imaging method for the diagnosis of enteric fistulas and an evaluation with MRI and colonoscopy can direct the most appropriate treatment. Indeed, asymptomatic fistulas do not require surgical intervention, but it is important to monitor the effect of medication because the inflammation might result in a more complicated disease in the long run[9]. The data on the most appropriate surgical approach for enteric fistulas are scarce. However, in recent years, there has been a tendency to preserve non-disease target organs as much as possible from excessive surgical resections, which are reserved for the diseased organ. Active CD could be complicated by an intra-abdominal abscess. Abscesses should be treated initially with antibiotics and when larger than 3 cm with percutaneous drainage (PD). Indeed, ultrasonography or computed tomography PD placement is a relatively safe procedure with rare complications and it allows to delay surgery. In the time between PD placement and surgery, the patient should be optimized by starting parenteral nutrition and broad-spectrum antibiotic therapy and discontinuing biological therapy, delaying the surgical timing by a few weeks. Conversely, emergency surgery without optimization or sepsis control with PD and antibiotics significantly increases the risk of stoma and it is associated with higher rate of post-operative complications[21].

Patient optimization

Nutritional deficiency is a common feature in patients with CD due to enteric fistulas, inflammation of the mucosa, and chronic diarrhea. A meta-analysis[22] has evaluated the impact of enteral and parenteral nutrition in a large cohort of patients with CD. Pre-operative enteral nutritional optimization reduced post-operative complications, especially decreased post-operative morbidity. Indeed, enteral feeding improves nutritional and immunological status with a lower risk of intra-abdominal infection or anastomotic leak after the surgery compared with undernourished patients[23]. A recent prospective study supported the aforementioned results with a 2-fold decrease rate of intra-abdominal septic complications and requirement for stoma in malnourished patients with a pre-operative enteral nutritional support compared with malnourished patients which underwent upfront ileocolonic resection for CD[24]. Latest ECCO guidelines[14] suggested enteral optimization before the surgery and considered parenteral nutrition when enteral nutrition is not tolerated, though the duration of pre-operative nutritional support is not standardized.

Reducing the surgical impact by a minimally invasive approach

Laparoscopic ileocolic resection has been increasingly used as a result of encouraging clinical studies demonstrating its superiority with regard to the open approach[25,26]. In fact, laparoscopic surgery provides reduced hospitalization, lower rates of post-operative complications, reoperations, and readmissions, and lower rates of incisional hernia compared with the open approach. Despite increased device-related costs, the reduced

indirect burden makes the laparoscopic approach more cost effective compared with the open approach[26]. In fact, has been included in the current guidelines as a standard of care for primary ileocolic resection[14].

Single-port (SP) laparoscopic surgery, introduced as an evolution of the laparoscopic approach, implies one single incision to perform the entire procedure and extract the specimen. The first comparative analysis of SP laparoscopy reported similar post-operative complication rates and reduced post-operative opioid analgesic requirement compared with multiport laparoscopy (MP)[27]. However, a more recent investigation[28] showed reduced post-operative pain and opioid analgesic consumption in the SP group compared with the multiport approach. These results were also confirmed by the study of Celentano et al.[29], which retrospectively compared SP with MP laparoscopy and open surgery. In that study, the open approach showed a 2-fold increase in post-operative complications compared with minimally invasive procedures and SP patients had a significantly shorter hospital stay compared with laparoscopy and open surgery. Despite the concerns on the use of SP in complex cases, preliminary data demonstrated its feasibility also for stenosing or fistulizing CD[30].

The robotic-assisted approach provides a potential benefit in abdominal surgery, allowing for a three-dimensional visualization, wristed instruments, and a stable camera platform. Few studies assessed the efficacy of robotic ileocolic resection compared with standard laparoscopy in CD. Overall, the current evidence consistently reports comparable postoperative complications rate and functional outcomes between the two approaches[31,32]. However, the increased costs limited the spread of robotic-assisted ileocecal resection for CD.

The use of *intraoperative near-infrared light and indocyanine green (ICG) fluorescence angiography* is largely used in colorectal surgery to identify the anastomotic level avoiding hypoperfused bowel and potentially reducing the AL rate[33]. The role of this technology in CD is not well investigated. Freund et al.[34] assessed in a retrospective study the role of intraoperative ICG during complex redo ileocolic resection among 12 patients compared with 24 patients who underwent redo ileocolic resection without ICG fluorescence evaluation. The authors did not find significant differences between the two groups in terms of post-operative complications. In addition, ICG perfusion assessment did not change the anastomotic site. The small number of patients and retrospective nature are important limitations of this study. However, further studies are necessary to evaluate the role of ICG fluorescence in CD[34].

Surgical strategies to reduce surgical recurrence

Although the traditional role of surgical innovation consists in improving the immediate postoperative outcomes, increasing preclinical evidence on the pathological mechanisms of CD triggered the development of innovative surgical techniques to prevent the post-operative recurrence of CD, shifting the main interest of surgeons from the early outcomes to the long-term outcomes of the disease.

Different anastomotic configurations after ileocecal resection in CD were described for restoration of intestinal continuity to reduce the rate of post-operative complications and recurrence. Muñoz-Juárez et al. compared wide-lumen stapled anastomosis (side to side) and end-to-end anastomosis after surgery for ileocolic resection in CD to investigate the post-operative outcomes[35]. The side-to-side group had fewer post-operative complications (6% vs. 13%) and a lower incidence of recurrent CD symptoms (24% vs. 57%) when compared with end-to-end anastomosis. A systematic review and meta-analysis of 11 trials and a total of 1,113 patients showed a reduction in terms of post-operative recurrence and reoperation when stapled side-to-side anastomosis was performed rather than handsewn end-to-end anastomosis[36]. Thus, stapled side-to-side anastomosis is considered an optimal anastomotic technique after intestinal resection for CD.

In 2011, Kono et al.[37] described an antimesenteric functional end-to-end handsewn anastomosis (Kono-S anastomosis) to reduce surgical recurrence at the anastomotic site. Kono-S anastomosis involves three principles: (a) mesentery preservation with mesenteric section close to the intestinal wall; (b) stapled resections of the pathological bowel site and consecutive suture of both the stumps to create a supporting column to prevent anastomotic distortion; and (c) longitudinal enterotomies on the antimesenteric site of the two stumps and a handsewn anastomosis (Fig. 1)[37]. A recent meta-analysis[38] - including nine studies and 676 patients – compared the Kono-S with conventional side-to-side anastomosis and found a significant decrease in the rate of 5-year surgical recurrence. The pooled analysis failed to demonstrate a reduced rate of endoscopic recurrence in the Kono-S group, although Kono-S patients displayed a lower mean Rutgeerts score

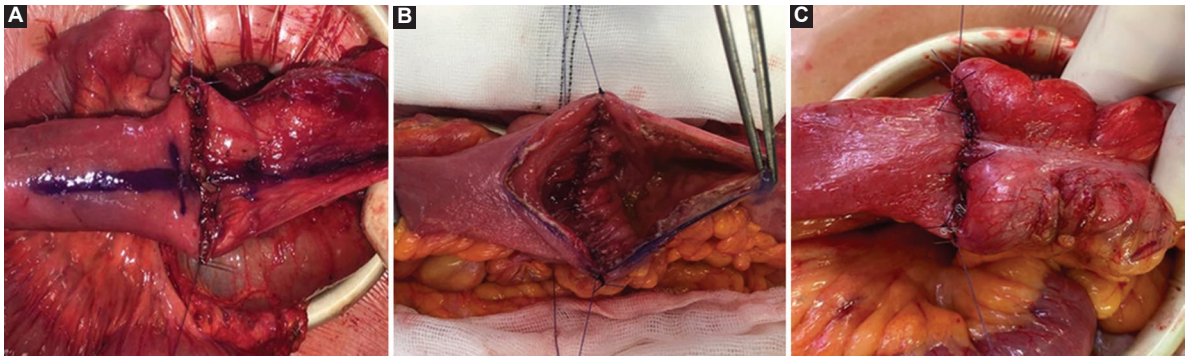

Figure 1. Kono-S anastomosis. **A:** stumps are sutured together to create the supporting column. **B:** longitudinal antimesenteric enterotomies 1 cm from the supporting column. **C:** handsewn anastomosis at the end of the procedure.

compared with the conventional anastomosis group. The rate of post-operative complications was comparable among the Kono-S and conventional anastomosis groups. Clinical recurrence was investigated only by the RCT from Luglio et al.[39], showing a significant reduction at 12 and 24 months. Kono-S anastomosis may reduce both clinical and endoscopic recurrence but further studies are needed to verify its feasibility and effectiveness: a multicenter randomized prospective trial promoted by the Weill Cornell Institute is currently ongoing and aims to compare Kono-S and standard side-to-side anastomosis (NCT03256240) (Table 1). In Kono-S technique, the mesentery – although manipulated – is preserved. However, recent studies pointed out the mesentery as a leading factor – rather than a mere target tissue – in the pathobiology of CD[40]. Mesenteric manifestations – including hypervascularization, fibrosis, thickness, and fat wrapping – correlate with CD activity and post-operative recurrence[40]. According to the classical model of CD pathogenesis, the mucosal damage is the primary event, which, in turn, provokes submucosal and mesenteric inflammation (outside-in model). In an alternative model, which emphasizes the role of the mesentery, the inflammatory process arises from the mesentery and the mesenteric nodes and the mucosal ulcerations are the terminal event (inside-out model)[41]. These observations led to hypothesize that a mesenteric resection close to the intestinal wall might provide reduced rates of clinical, endoscopic, and surgical recurrence compared with a partial excision[42]. The first study comparing mesentery resection versus mesentery sparing in ileocolic CD patients provided encouraging results with reduced rates of endoscopic and surgical recurrence – but the limited sample size prevented conclusive evidence[42]. These promising results were recently confirmed by a comparative analysis on CD patients undergoing colorectal resection: subjects receiving extensive mesenteric resection showed better surgical recurrence-free survival compared with those receiving limited mesenteric resection[43]. Due to technical difficulties and concerns regarding intraoperative bleeding[42], mesenteric excision is still underused but a growing number of randomized clinical trials has been initiated to further explore the safety, feasibility, and effectiveness of this technique, including one multicentric trial promoted by the University of Amsterdam (SPICY), one promoted by the Cleveland Clinic (SPARES), and one promoted by the Jinling Hospital in China (Table 2)[44]. In conclusion, despite recent progress in surgical procedures related to the role of the mesentery in CD, both mesentery excision and Kono-S anastomosis with mesentery manipulation and preservation have proved to be effective to reduce CD recurrence after bowel resection. The aforementioned findings question what is the best surgical approach in case of intestinal resection and bowel restoration, therefore, additional studies are necessary to better understand the pathogenesis of CD recurrence and to provide more effective surgical techniques in CD.

Proctectomy in CD

Non-restorative proctectomy usually is performed in patients with severe CD proctitis refractory to medical treatments associated to perianal disease. Because of the benign nature of the disease, a complete lymph node harvest is not mandatory and a close rectal

Table 1. Summary of Kono-S ongoing studies

Name of study	Type of study (country)	Primary aim	Study status (estimated completion date)	ClinicalTrials ID
"Study of the Kono-S Anastomosis Versus the Side-to-side Functional End Anastomosis"	RCT – Multicenter (Belgium, Finland, Germany, Italy, United States)	Post-operative recurrence of CD between Kono-S and side-to-side functional end anastomosis	Recruiting (December 2026)	NCT03256240
"Surgical Prevention of Anastomotic Recurrence by Excluding Mesentery in Crohn's Disease (SuPREMeCD)"	RCT – Single center (Italy)	Post-operative outcomes between patients with Kono anastomosis and patients with stapled side-to-side anastomosis	Recruiting (November 2022)	NCT02631967

Table 2. Summary of extensive mesenteric excision versus limited mesenteric excision ongoing studies

Name of study	Type of study (country)	Primary aim	Study status (estimated completion date)	ClinicalTrials ID
"The MESOCOLIC Trial: Mesenteric Excision Surgery or Conservative Limited Resection in Crohn's Disease"(38)	RCT – Multicenter (China, US, Ireland)	Rate of postoperative progression following extensive mesenteric excision (EME) and limited mesenteric excision (LME) in CD	Recruiting (January 2025)	NCT03769922
"Mesenteric SParIng Versus Central mesenterectomY in Ileocolic Resection for Terminal Ileitis in Crohn's Disease (SPICY)"	RCT – Multicenter (Nederland)	Endoscopic recurrence following a mesenteric sparing VS a central mesenterectomy for CD	Recruiting (September 2022)	NCT04538638
"MeSenteric SpAring Versus High Ligation Ileocolic Resection for the Prevention of REcurrent Crohn's DiseaSe (SPARES)"	RCT – Multicenter (Canada, Italy, United Kingdom, United States)	6-month endoscopic recurrence between high ligation of ileocolic artery or mesenteric sparing for terminal ileal CD	Recruiting (December 2021)	NCT04578392

dissection – leaving mesorectum *in situ* – could be performed to reduce nerves lesions and to minimize post-operative pelvic empty space. However, a retrospective study has shown that proctectomy with total mesorectal excision in CD has significantly lower perineal complications and higher healing rates compared with close rectal dissection. These results are attributable to the pro-inflammatory role of the mesorectum in CD. Indeed, high presence of tumor necrosis factor α-producing CD14+ macrophages and less expression of wound-healing marker were funded in mesorectal tissue of CD patients[45]. Transanal approach might be feasible and has been demonstrated safe when performing proctectomy for CD[46]. Indeed, advantages of the transanal approach are mainly present in patients with a narrow pelvis. However, this approach for proctectomy in CD could be demanding due to the inflamed and bulky mesorectum causing difficult planes[46]. Restorative proctectomy and ileal pouch–anal anastomosis (IPAA) for refractory pancolonic CD could be considered in selected patients in the absence of small bowel and perianal disease, due to the high risk of pouch failure in CD patients[14]. Panis et al.[47] compared a cohort of CD-IPAA patients with a cohort of ulcerative colitis (UC)-IPAA patients. Short-term post-operative outcomes were similar between the two groups, but definitive ileostomy and pouch removal rates after 5-years were significantly higher in the CD group. The same results were shown in a large meta-analysis of 3103 patients[48]. CD-IPAA patients had a likelihood 6 times higher of pouch failures and poorer functional outcomes when they were

compared with UC-IPAA patients[48]. Several treatments for pouch failure have been proposed over the years (i.e., pouch strictureplasty and endoscopic balloon dilatation in case of strictures and infliximab treatment for active CD of the pouch)[49]. Although, rescue surgery is not indicated in this group of patients and defunctioning ileostomy or pouchectomy with definitive ileostomy is the only recommended surgery to reduce post-operative complications[9].

Anorectal surgery for CD

PFCD manifests in up to 40% of CD patients[50]. Surgical management combined with anti-TNF treatment is the currently recommended approach for PFCD and allows for acceptable healing rates. The surgical approach to PFCD varies according to the anatomy and severity of the fistula: simple fistulas – either superficial, low, or with a single external opening – can be treated with a fistulotomy and – in selected cases – medical therapy may be avoided; complex fistulas – high, with single or multiple external openings, with or without rectovaginal involvement or proctitis – yield more challenging procedures. Complex fistulas often require multiple surgical interventions and have a lower rate of complete healing compared with simple fistulas. The first aim of the surgical intervention is to control the perianal sepsis. Once the acute infection is resolved, different surgical strategies may be applied to promote the healing, while preserving the sphincter function[5].

In recent years, new surgical strategies were developed to treat PFCD. However, a small subset of patients with refractory PFCD requires fecal diversion (FD) with a subsequent medical optimization. Singh et al. performed a meta-analysis among a total amount of 16 cohort studies including 556 patients to evaluate the effectiveness and long-term outcomes in patients treated with FD for PFCD[51]. More than half of the patients (63.8%) had an early clinical response after FD. Restoration of bowel continuity was attempted in 34.5% of patients and operation was precluded for the remaining patients due to the poor PFCD response or patient preference. Approximately 26% of patients who underwent bowel restoration required a rediversion for severe perianal disease relapse and 41.6% of patients required proctectomy due to the persistence of symptoms. Absence or improvement of rectal disease was the main factor associated with good outcomes after bowel restoration[51].

Indeed, active luminal disease and proctitis are related to low rate of PFCD healing and a higher proctectomy rate (29-77.6%)[52]. A global consensus of PFCD considered active luminal disease as an indication for aggressive medical treatment avoiding surgical procedures[52].

Ligation of intersphincteric fistula tract (LIFT) procedure was proposed to achieve fistula closure. In 2017, a retrospective evaluation assessed 23 patients with PFCD treated with LIFT[53]. Fistula healing was observed in 11 patients (48%) and the overall median time of LIFT failure was 8 months. LIFT may provide a low fistulae recurrence rate and with incontinence, but further studies are needed to demonstrate its effectiveness in PFCD.

Fibrin glue is a topical biological adhesive that mimics the physiological process of coagulation and takes advantage of the activation of thrombin to form a fibrin clot, thus inducing the mechanical sealing of the fistula tract. In a multicenter randomized trial comparing fibrin glue[54] with no treatment after seton removal, clinical remission was observed in almost 38% of patients treated with fibrin glue compared with 16% in the observation group. Despite its randomized design, this study had some relevant limitations: the small sample size and the use of an inactive comparator prevented a generalizable conclusion about the effectiveness of fibrin glue. Fibrin glue may be a simple, well-tolerated, and effective treatment for fistula in CD.

Video-assisted anal fistula treatment (VAAFT) is a sphincter-sparing approach, involving a diagnostic phase and an operative phase using a fistuloscope. The main advantage of the VAAFT procedure is the possibility of intraoperatively identify additional undetected fistula tracts, avoiding extensive perianal wounds[55]. However, VAAFT is a costly procedure, requiring a long learning curve to achieve proficiency.

In the past years, increasing evidence has focused on the feasibility and efficacy of *mesenchymal stem cells treatment (MSCs)* in perianal CD. MSCs can be obtained from cellular aspirate of human adipose or bone marrow tissue and differentiate in different types of cells, favoring the tissue regeneration and modulating the immune response[56]. ADMIRE-CD trial, a randomized double-blind placebo-controlled trial that assessed the effect of MSCs compared with placebo to treat PFCD, reported at 24 weeks a higher rate of complex PFCD healing in the MSCs group than in placebo (50% vs. 34%; $p = 0.024$)[57]. These results were confirmed in a second study after 52-week follow-up with a fistula healing in 56.3% in the MSCs group compared with 38.6% in the control group ($p = 0.01$)[58]. A second placebo-controlled trial to assess the efficacy and safety of darvadstrocel (Cx601) for the treatment of PFCD is underway (NCT03279081). The most recent meta-analysis[59] on the topic identified almost 24 randomized controlled trials and cohort studies comparing placebo (or fibrin glue injection) with

MSCs in both CD and cryptoglandular fistula, reporting a higher healing rate compared with conventional therapies. Interestingly, CX601 seemed more effective compared with homemade cultures, suggesting that a standardized systematic protocol for MSCs production plays a pivotal role in determining the therapeutic potential of MSCs[59]. In complex perianal fistula, MSCs treatment showed significantly higher healing rates compared with placebo administration, either alone or combined with fibrin glue injection. A subgroup analysis restricted to either autologous or allogeneic MSCs showed similar results with higher healing rates compared with placebo. A subgroup analysis on adipose-derived MSCs also showed more effective outcomes compared with placebo. Overall, MSC administration may be a safe and efficacious treatment to promote fistula healing in PFCD but – despite the encouraging results – a substantial heterogeneity exists among the several Phase I, II, and III clinical trials, using different MSCs donors (autologous or allogenic), source tissues (bone marrow or adipose tissue), administration timing, and doses. The high heterogeneity among the protocols and the inhomogeneous definition of fistula healing may prevent a conclusive recommendation in favor of MSCs treatment, particularly for complex CD fistula, and further studies – focusing on the biological mechanisms – are needed on the topic. Despite the comparable efficacy, allogenic adipose-derived MSCs are preferred with respect of bone marrow-derived MSCs, due to the easier isolation and higher yield. However, regardless of the origin source, the need for cultured expansion processes makes autologous and allogeneic MSCs production costly and time consuming. The possibility of obtaining adipose-derived MSCs from mechanically treated human adipose tissue – thus avoiding the cultured expansion step – has risen consistent interest in the past years. A recent prospective study[60] demonstrated – in a small number of patients – the feasibility and safety of local injection of autologous microfragmented adipose tissue to treat PFCD. Autologous harvested fat was processed using a marketed system (Lipogems system®) which provided microfragmented adipose tissue removing the pro-inflammatory residues. The results of the study – although very preliminary – suggest that microfragmented adipose tissue injection may be a valid treatment for PFCD.

Conclusion

Surgery may be required in case of medically refractory patients or fibrostenosing and fistulizing disease. The main goal of the surgical treatment is to resolve the disease-related complications; however, several technical strategies may be implemented to improve the postoperative outcomes, reduce the post-operative complications, shorten the patients' recovery, and extend the disease remission. In the past years, significant steps forward have been made in the surgical management of CD but further research is needed to integrate these innovative strategies in the clinical practice.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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