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When can we cure Crohn's?

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A B S T R A C T

Crohn's disease is a life-long idiopathic inflammatory disease which affects the entire gastrointestinal tract and occasionally extra-intestinal organs. CD is thought to result from complex interactions between environmental factors, the gut microbes, and the genetic background and the immune system of the host. In the last decades research on these pathogenetic components, and especially on mucosal immunity, has led to the development of biologic agents and therapeutic strategies that have improved dramatically the treatment of CD but we are still far away from curing the disease. If there is a treatment for CD that will probably evolve through methodical steps towards integrating research on all the components involved in the pathogenesis of CD. This holistic and global approach may aid at unravelling the mysteries of CD and developing novel agents and therapeutic strategies which by targeting multiple pathogenetic pathways and at different stages of disease may lead hopefully to cure.

Introduction

The recent English edition of Wikipedia defines 'cure' as 'the end of a medical condition; the substance or procedure that ends the medical condition, such as a medication, a surgical operation, a change in lifestyle, or even a philosophical mindset that helps end a person's sufferings'. Crohn's disease (CD) is an idiopathic, granulomatous, life-long disease that affects any part of the

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gastrointestinal tract from the mouth to the anus and runs a relapsing-remitting or continuously active course. In up to 35% of the patients the disease affects one or more extra-intestinal organs [1]. CD can impair profoundly the quality of life and can cause significant functional and/or psychological disability [2]. Despite remarkable improvement in the medical treatment there is still no definitive therapy for CD. Current therapeutic interventions aim at inducing and maintaining clinical and biologic remission of active disease and healing of lesions in order to restore quality of life to near normal levels and prevent complications which may lead to intestinal failure and disability [3]. Surgery is reserved for disease complications. In the text to follow, we shall review briefly what we have learned since the first descriptions of disease, what the major obstacles to curing CD are and how these can be overcome, and, finally we will discuss whether cure is a realistic option.

What have we learned since the first description of CD?

Eighty years after Crohn, Ginzburg and Oppenheimer presented their landmark article [4] we have improved substantially our understanding of the pathophysiology and the natural history of CD. CD is now thought to develop in genetically susceptible individuals from complex but as yet unknown interactions between various environmental factors, the gut microbes (gut microbiota) and the mucosal immune system of the host [5]. These interactions determine the clinical phenotypes and the natural course of the disease. We have also made remarkable achievements in the treatment of various subtypes of CD.

Due to advances in molecular biology, genetics and tissue staining techniques in association with easy sampling of biologic fluids and intestinal tissues 'bench to bedside' research on the immune system of the host grew disproportionally faster than research on other pathogenetic components of CD. Defective innate immunity and pathogenic effector T helper cells were considered as the driving forces for disease activation and progression. A network of cells, key-inflammatory mediators, and pro- and anti-inflammatory immune pathways were implicated in the immunopathology of CD. Defective immune regulations and apoptotic mechanisms were incriminated for the accumulation of inflammatory cells and the perpetuation of chronic inflammation [6–10]. Despite limitations, this feverish research led to the discovery and production of novel therapeutic agents, initially anti-TNFα biologics and recently anti-integrins, which target selectively key inflammatory mediators. The efficacy and safety of these agents has been elucidated in large, adequately powered randomized controlled trials (RCTs) with harder end points than simple clinical remission [11–16]. A long pipeline of non anti-TNFα biologic agents is currently being investigated in phase II and III RCTs and is expected to further expand the pool of future therapeutic options [17–19]. Additional therapeutic interventions, such as granulocyte/monocyte apheresis [20], and autologous or allogeneic mesenchymal or haematopoietic stem cell transplantation [21–23] are also currently under investigation. Furthermore, pharmacokinetic studies have facilitated the initiation of therapy with appropriate doses of single drugs and/or drug combinations, monitoring the response and adherence to treatment, and optimizing therapy to ensure maximum efficacy and safety [24,25]. Modern imaging modalities allow better localization and grading of disease activity and severity. Factors predicting a disabling course of CD have been identified and call upon earlier therapeutic interventions to prevent irreversible bowel damage. Thus, we are now able to deliver highly individualized therapies based not only on disease profile but also on efficacy and safety of medications and on important elements of patient profiles. A 'treat-to-target' strategy is evolving which marries the concepts of early intervention and regular assessment of disease activity to ensure optimal control of disease using objective serological and faecal markers of inflammation and mucosal healing as surrogate markers of sustained 'deep' remission of CD [3]. This strategy promises excellent mid-term therapeutic outcomes, including reduced rates of hospitalizations and surgery, improvement in health-related quality of life and avoidance of disability.

Intensive research has documented the important role of each of these pathogenetic components of CD. Epidemiological studies have identified amongst others particular risk factors for developing CD and for a disabling course of disease; geographical gradients in the prevalence of disease; and, a dramatic increase in the incidence when former underprivileged societies adopt western dietary- and life-styles and improve hygienic conditions [1,26]. A 'clean-environment', linked to the hygiene hypothesis, elimination of helminthes, extensive and repetitive use of antibiotics in early life, infections,