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New treatments in inflammatory bowel disease — A thrilling time ahead

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Except for some surgical techniques, up to 1940 the clinical course of inflammatory bowel disease was determined by its own natural history: most medical interventions even worsened prognosis (1). The empyrical introduction of salazopyrine early in the 1940s, pioneered by Nanna Svartz in Sweden (2), was followed relatively soon by the incorporation of corticosteroids during the 1950s (3). However, it took both a long time to reach patients, and quality scientific evidence to better establish their

indications built up very slowly (1). Surgery progressed, anesthetic procedures became increasingly safer, and medical advances in antibiotic therapy and nutrition improved care for our patients. Over two decades thiopurines, methotrexate, cyclosporin and tacrolimus were incorporated, and mesalazine was shown to be the active molecule in salazopyrine. In any case, establishing the *whom, how and when* for therapeutic methods was the most challenging part. Sidney Truelove's team at Oxford developed the most relevant concepts, as well as a school whose students spread all throughout the world, particularly around Europe. Nevertheless, advances occurred with a tempo we might describe as *adagio molto,* easy to assimilate by clinicians but exasperatingly sluggish for most patients (1,4).

In 1975 César Milstein and Georges Köhler reported their method to obtain monoclonal antibodies (5). In 1998, *only* 23 years afterwards, infliximab revolutionized the treatment of rheumatoid arthritis and Crohn's disease (6). Scientific and technological advances made possible the incorporation of additional anti-TNF agents (7) and, more importantly, an increase in therapy targets; a few years later vedolizumab (8), an antibody against integrin $\alpha4\beta7$, and ustekinumab (9), an anti-IL12 (and anti-IL23) agent, expanded the available options. The development of regulatory agencies and of the evidence-based medicine approach contributed to a complete change in methodology: clinical trials and meta-analyses gradually acquired a leading role. The way was not free from obstacles such as failures because of unexpected adverse events (as was the case with natalizumab) (10) or the delayed use of infliximab for ulcerative colitis, mainly due to mistaken preconceived notions (11). The number of patients increased so much over the last 50 years (12) that business expectations also became a key motor for the development of newer drugs, as well as for increased associated costs (13).

After a few years in which the tempo sped up slightly to an *andante con moto*, scientific advances in immunology, biochemistry, bioinformatics and pharmacology, and multi-million reinvestments of earnings in association with a growing market, have led us all to get the feeling of having reached an *allegro con brio*. In a relatively short time, within less than 10 years, Janus kinase (JAK) inhibitors (tofacitinib [14], filgotinib [15], upadacitinib [16,17]), anti-IL23 antibodies (risankizumab [18,19], mirikizumab

[20], guselkumab [21]), and S1P modulators (ozanimod [22], etrasimod [23,24]). This means that new therapies with distinct, innovative mechanisms of action are now available; that, again, we can administrate drugs through the oral route; and that possible choices have increased (25). Furthermore, biosimilars (26) have changed the market, generally improving accessibility, and drug administration routes for already experienced agents have diversified with subcutaneous infliximab and vedolizumab, this being the anteroom to a future also exciting with regard to administration routes (27).

While the results for each individual drug fail to be spectacular (in initial studies, for instance, results were nowhere near the remission figures obtained for psoriasis [28,29]), thrilling possibilities lie ahead. Really diverse options are available, and our imagination may now contemplate all sorts of either simultaneous or sequential combinations (30). Some newer combinations have already shown their potentiality. Furthermore, experience has shown that getting to understand each drug's clinical properties may well take lustra, opening up the possibility of highly diverse treatment patterns at some point in the future (18).

However, despite a far better outlook, some of the same issues remain — we have lots of "*whats"*, but the *whoms, hows and whens* are still lacking good answers (31). Our ability to predict each patient's response to each drug in each clinical scenario is virtually nil. Although precision medicine is exciting, the fact is that systematic application in daily clinical practice remains far off (32). We must thoroughly improve our clinical research methods to not miss the huge amount of information that might be obtained by wisely using the data collected in daily practice from the millions of patients who suffer from IBD (33). We need directly comparative studies. Some of their results are surprising — less may be more in immunology, and blocking only IL23 may be better than simultaneously blocking Il12 and IL23 in Crohn's disease (34). Nevertheless, we must clearly abandon the so-called step-up strategies as "standard" in order to embrace strategies based on each person's needs under each set of circumstances, and of course we must forget the old "conventional treatment" concept promulgated by the prescribing information of infliximab, which inexplicably persists. It is high time that "advanced" drugs be deemed "conventional" following 25

years' experience and the amazing data provided by the PROFILE study (11,35).

Perhaps the most thrilling aspect of the future remains to be mentioned. All the above lines are aimed at modulating the immune system, one of the orchestra musicians, maybe a professor, the concertino or the conductor. The outburst in the incidence of the disease sure has environmental causes (36). Factors such as microbiota, diet, widespread use of antibiotics during childhood, use of refrigerators, and tobacco smoking or pollution also contribute to orchestral production. While our knowledge on these areas is rapidly growing, the enormous complexity of their interactions makes it challenging to select potential therapy targets and ways to affect them. Some experiences point to dietary ways (37), and the microbioma (38) or even psychotherapy (39) will be key in the future, even though advances in immune system modulation (for instance, using oral antibody inhibitors [40], cell therapies [41], or agents with anti-fibrotic action [42] or new mechanisms of action [43,44]) will continue to expand available options. Perhaps unexpected guests will change our outlook completely (45-47).

We cannot finish without mentioning that mere availability of therapies does not mean that these will reach the patients. From my perspective, the greatest advance in the treatment of inflammatory disease has been professional specialization and dedication through the setup of interdisciplinary care units, which may be improved by making them more translational in nature, by incorporating other views into the process (48). The greatest limitation, however, resides with lack of accessibility to treatment (49). Time is too long from indication approval by regulatory bodies to patients benefiting therefrom, sometimes because of local barriers for the sake of an alleged, never demonstrated *efficiency*. However, inflammatory bowel diseases are a global problem, and the access issue is much more severe in most of the world's geography. As physicians, we must strive to eliminate poverty, to break down barriers, to improve life for all patients, not just ours (50). We must not abandon our duty as political activists, following our greater masters such as Rudolf Virchow (51). The best medicine is a society that is fair, and human society is a global affair.

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