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REVIEW

New molecules in the treatment of inflammatory bowel disease☆

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Abstract Inflammatory bowel disease (IBD) is a disorder of unknown aetiology that provokes chronic inflammation of the gastrointestinal tract. Anti-tumour necrosis factor drugs have represented a major advance in the treatment of IBD patients in the last few years and also have a good safety profile. Nevertheless, these treatments are not effective in all patients and, in initial responders, there can be a loss of response in the long-term. Consequently, new treatments are needed for IBD, aimed at distinct therapeutic targets.

In the last few years, new molecules have been incorporated into the therapeutic armamentarium of IBD patients. Golimumab is an anti-tumour necrosis factor monoclonal antibody with demonstrated effectiveness in the treatment of ulcerative colitis. The use of CT-P13 (biosimilar infliximab) has been approved in Europe for the same indications as the original infliximab. More recently, vedolizumab, an anti-$\alpha 4\beta 7$ integrin monoclonal antibody, has been approved for the treatment of Crohn's disease and ulcerative colitis. A large number of molecules are currently under development, some of which will, in the future, broaden the therapeutic options available in the treatment of IBD patients.

Finally, in the next few years, studies should aim to identify factors predictive of response to the distinct biological agents for IBD in order to allow personalised selection of the best therapeutic alternative for each patient.

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Nuevas moléculas en el tratamiento de la enfermedad inflamatoria intestinal

Resumen La enfermedad inflamatoria intestinal (EII) es un trastorno de etiología desconocida consistente en una inflamación crónica del tubo digestivo. Los fármacos dirigidos contra el factor de necrosis tumoral han representado un hito en el tratamiento de los pacientes con EII en los últimos años contando además con un buen perfil de seguridad. No obstante, estos tratamientos no son eficaces en todos los pacientes y, en aquellos que responden inicialmente, se ha descrito una pérdida de respuesta a lo largo del tiempo. Por estos motivos, es necesario el desarrollo de nuevos tratamientos para la EII, dirigidos hacia diferentes dianas terapéuticas.

En los últimos tiempos se han incorporado nuevas moléculas al arsenal terapéutico de los pacientes con EII. El golimumab es un anticuerpo monoclonal que se dirige contra el factor de necrosis tumoral y que ha demostrado ser eficaz en el tratamiento de la colitis ulcerosa. Asimismo, ha sido aprobado en Europa el uso de CT-P13 (infliximab biosimilar) para las mismas indicaciones que el infliximab original. Más recientemente, vedolizumab, un anticuerpo monoclonal dirigido frente a las integrinas $\alpha 4\beta 7$ ha sido aprobado para el tratamiento de la enfermedad de Crohn y la colitis ulcerosa. En la actualidad se están desarrollando un gran número de moléculas, algunas de las cuales vendrán, en un futuro, a ampliar las opciones terapéuticas en los pacientes con EII.

Finalmente, en los próximos años los estudios deberán ir dirigidos a identificar factores predictores de respuesta a los distintos fármacos biológicos para la EII con el fin de seleccionar, de forma más personalizada, la mejor alternativa terapéutica para cada paciente.

Introduction

Inflammatory bowel disease (IBD) is a chronic disorder of unknown aetiology that involves a pathological response of both the innate and acquired immune system, leading to chronic inflammation of the gastrointestinal (GI) tract. It is the result of the interaction of various factors, including genetic susceptibility, environmental factors, infectious agents, commensal enteric flora and immune disorders.[1,2] The wide range of factors involved in the development of the disease, together with the complexity of the immune system, present multiple therapeutic targets, which are reflected in the large diversity of molecules that have been evaluated as potential treatments for IBD.

The era of biological therapy in the treatment of IBD began in 1998, when the United States Food and Drug Administration approved infliximab for the treatment of patients with Crohn disease.[3–5] Many new biological drugs have been developed and approved since then, all of which have so far targeted tumour necrosis factor-alpha (TNF). Anti-TNF drugs have been a milestone in the treatment of patients with IBD in recent years, reducing the need for surgery and hospital admission and, most importantly, improving quality of life; they also have a good safety profile. Nevertheless, these treatments are not effective in all patients, and loss of response over time has been described in initial reponders.[6–8] Furthermore, although they are safe in general, they are associated with adverse effects and are expensive.

For these reasons, new treatments with a more specific mechanism of action directed at different therapeutic targets must be developed for IBD, in order to achieve a more local effect in the inflamed organ.

Three new molecules have recently been added to the IBD therapeutic arsenal: golimumab and CT-P13 (infliximab biosimilar), which are anti-TNF drugs, and vedolizumab, which inhibits lymphocyte migration to the tissues of the GI tract by blocking the $\alpha 4\beta 7$ integrin.

The aim of this review is to make a practical, critical appraisal of the biological molecules recently approved for the treatment of IBD, their characteristics, dosage, indications and safety profile. Finally, we will briefly present some of the groups of molecules being developed for the treatment of IBD.

Golimumab

Golimumab (Simponi, Janssen Biotech, Inc., Horsham, PA, United States) is an alternative anti-TNF monoclonal antibody for patients with ulcerative colitis (UC) refractory to conventional treatment. Golimumab was approved in the United States by the Food and Drug Administration in May 2013; more recently, in October 2013, the European Medicines Agency (EMA) approved golimumab for the treatment of patients with UC who have been refractory or intolerant to conventional treatments.