Biological therapies in autoimmune chronic inflammatory diseases (ACIDs)

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Abstract. – Autoimmune chronic inflammatory diseases (ACIDs) represent a growing part of chronic diseases and their cellular and molecular pathways have been deeply investigated in recent years in order to disclose some clue aspects that could be optimal targets of specific therapies. Among the autoimmune rheumatic diseases a major molecular driver was discovered (TNFα) which represents along with IL1β, a key driver of the ongoing chronic inflammation. The same molecule arose as a major player in the pathological mechanism of Crohn’s disease. The biomolecular pathways of Ulcerative Colitis appear more complex and not yet defined, although targeting specific integrins (α4β7) has shown some promises, pending the severe side effects related to treatment.

Key Words: Spondyloarthropathies, Crohn’s, Ulcerative colitis, TNFα blockers, α4β7 integrin.

Introduction

Autoimmune chronic inflammatory diseases (ACIDs) are frequent affecting as much as 5% of the general population. Some of the inflammatory diseases present a clear-cut loss of tolerance with the appearance of specific autoantibodies (Systemic Sclerosis, Systemic Lupus Erythematosus, Sjogren’s), others present a less specific loss of tolerance leading to the appearance of very common, almost natural, autoantibodies (Rheumatoid Arthritis, Undifferentiated Connective Tissue Disease), whereas some less common diseases present, frequently, antibodies against foreign bacterial components, that lead to interpret the chronic inflammation as determined by a previous infection. In these cases it can be hypothesized that there is a defect in the natural immunity that cannot fully clear infectious agents.

Among the chronic inflammatory disease, rheumatic diseases and inflammatory bowel diseases are by far the most important ones. Their prevalence is quite different, but their impact on the quality of life and on the costs of the health care system is very similar in terms of impact/patient/year (Table I).

Relationship Between Mucosal Immunity, Inflammatory Bowel Diseases and Spondyloarthropathies

The relationship between chronic inflammatory rheumatic diseases and inflammatory bowel diseases (IBD) is certainly very strict as demonstrated by the co-existence of spondyloarthropathies and IBDs (either Crohn’s disease as well as Ulcerative Colitis). This suggests that common genetic and immunological pathways govern the pathogenesis of both disease phenotypes. In addition many patients without clearcut evidences of IBDs, do have microscopic colitis when assessed histologically. Therefore the association between colonic inflammation and spondyloarthropathy is common.

One of the common interesting aspects is the genetic predisposition in all the autoimmune chronic inflammatory diseases and inflammatory bowel diseases (IBD) is certainly very strict as demonstrated by the co-existence of spondyloarthropathies and IBDs (either Crohn’s disease as well as Ulcerative Colitis). This suggests that common genetic and immunological pathways govern the pathogenesis of both disease phenotypes. In addition many patients without clearcut evidences of IBDs, do have microscopic colitis when assessed histologically. Therefore the association between colonic inflammation and spondyloarthropathy is common.

One of the common interesting aspects is the genetic predisposition in all the autoimmune chronic inflammatory diseases and inflammatory bowel diseases. This is the case of B27 related diseases. Moreover it has recently been shown that psoriatic arthritis (PsA) and Crohn’s disease (CD) share a common association with an organic cation transporter (OCTN) gene cluster, comprising a single nucleotide polymorphism (SNP) in exon 9 of SLC22A4, and a promoter polymorphism in the adjacent gene SLC22A5. These findings suggest a common pathogenetic pathway,
Table I. Prevalence of some autoimmune chronic inflammatory rheumatic diseases and of the two most common bowel inflammatory diseases in Italy.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>%</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>0.46</td>
<td>(0.33-0.59)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>0.42</td>
<td>(0.31-0.61)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>0.37</td>
<td>(0.23-0.49)</td>
</tr>
<tr>
<td>Crohn’s</td>
<td>0.05</td>
<td>(0.02-0.07)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>0.07</td>
<td>(0.05-0.08)</td>
</tr>
</tbody>
</table>

Many small molecules, representing conventional therapeutic approaches, act through induction of apoptosis. After and along with glucocorticoids (GC), mainly controlled ileal release budesonide, which represents the golden key to achieve the control of disease activity in the induction phase of any therapy. Sulphasalazine (SSZ) has successfully been used because it is a potent inducer of T cell apoptosis, Azathioprine (AZA) can induce apoptosis in CD28-stimulated T cells by specific blockade of Rac1 activation, and thalidomide can induce apoptosis in human monocytes14. Even Methotrexate (MTX) which exerts a potent anti-proliferative response on autoreactive T cells, proved to be effective in steroid resistant cases as a maintenance treatment and as a therapeutic tool in GC resistant cases. Weekly intramuscular injections of 25 mg MTX induced remission in about 40% of patients twice the placebo rate15. The real new avenue is represented by the biological drugs acting on some of the key molecules driving the local inflammatory ulcerative lesions, among which TNFα is the key driver. As in Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), TNFα, soluble and membrane, targeted therapies profoundly modified the therapeutic approach in the last years. This innovative approach helped to more fully understand the biological basis of the ulcerative lesions, since it clearly arose that blocking the soluble form of TNFα, without acting on the membrane form, did not affect the disease. Therefore only the
blockade of both isoforms of TNFα (soluble and membrane) allows to control CD not fully managed with budesonide and AZA. Another important information coming out from trials was that the chimeric monoclonal (Infliximab) could maintain its effectiveness provided that immunosuppressors are given simultaneously in order to decrease the immunogenicity of the monoclonal. In UC, the mainstay of therapy for induction of remission and to prevent relapses is represented by other small molecules, the Aminosalicylates (ASA) along with GC, other than budesonide. Among the immunomodulators, Cyclosporine A (CsA) has proved to be very useful especially through the i.v. route as an induction treatment. As a maintenance, AZA along with GC, other than budesonide and membrane) allows to control CD not fully managed with budesonide and AZA. Among the immunomodulators, Cyclosporine A (CsA) has proved to be very active, especially through the i.v. route as an induction treatment. As a maintenance, AZA has shown to be useful especially in the extensive treatment. As a maintenance, AZA has shown to be useful especially in the extensive disease much less in left sided disease. Contrarywise from CD, the rationale for treating patients with TNFα blockers (Infliximab), based on the high TNFα synthesis by mucosal T cells, high TNFα levels in the stool, and urine, arose less clearly when randomized trials were performed in GC resistant or refractory patients. More success was achieved by using RDP58 a novel anti-inflammatory decapetide that blocks TNFα, but it also inhibits IFNγ, IL2 and IL12. More promising approaches appear to be the biologicals acting on T cells or their products, mainly anti-IL2 monoclonals (Daclizumab, a recombinant humanized immunoglobulin G1 directed against CD25, the IL2 receptor or Basiliximab a chimeric monoclonal also directed against CD25) which proved efficacious in inducing remission along with GC, or with Visilizumab, a humanized antibody with a mutated immunoglobulin G2 Fc region directed at the CD3 chain of the T cell receptor. Anti-leukocyte adhesion therapies in UC, attracted investigators and trials with Natalizumab, a monoclonal to the α4β7 integrin were performed with clinical success. The occurrence of leukoencephalopathies due to reactivated polyomaviruses infections in patients with Crohn’s disease, very likely will forbid their employment in clinical practice. Several other biologicals are under scrutiny in the clinics (IFNβ, enemas of epidermal growth factor–EGF, etc) given the high number of potential molecular mediators of damage or of repair, one time will tell us whether, like in Rheumatology we will see a proliferation of several compounds that have the potential to be used or in combination or even in succession.

References

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