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# Treatment of spondyloarthritis beyond TNF-alpha blockade

Filip Van den Bosch [a, *], Atul Deodhar [b]

[a] Department of Rheumatology, University of Ghent, Ghent, Belgium
[b] Division of Arthritis & Rheumatic Diseases (OP09), Oregon Health & Science University, Portland, OR, USA

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A B S T R A C T

The advent of biologics targeting tumor necrosis factor-alpha (TNF-alpha) has revolutionized the field of rheumatology in general and the treatment of spondyloarthritis (SpA) in particular, since – apart from non-steroidal anti-inflammatory agents – no disease modifying treatments are available for this frequent, inflammatory rheumatic condition. The significant improvements in signs and symptoms observed with TNF-blockers in this group of diseases, have raised the bar with regard to treatment goals, including clinical remission. Even if treatment failure with TNF-blocking agents may be a relatively rare phenomenon, cases of primary non-responders, secondary loss-of-efficacy and intolerance, have been described. Results with abatacept, rituximab and tocilizumab – all effective in the treatment of rheumatoid arthritis – were disappointing, especially in patients that had previously failed anti-TNF therapy. On the other hand, there is increasing evidence that targeting the cytokines of the $T_h$-17 axis is associated with major improvements of skin psoriasis and its associated arthritis. In axial spondyloarthritis, preliminary proof-of-concept studies with ustekinumab and interleukin-17 targeting therapies suggest that these agents could become the first new treatment options, not targeting TNF. Finally, the advent of small molecules targeting inflammatory, intracellular signalling pathways, may further change our future therapeutic approach.



* Corresponding author.
*E-mail address:* filip.vandenbosch@ugent.be (F. Van den Bosch).

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## Introduction

Over the last decade, the treatment of spondyloarthritis (SpA) has undergone a radical change from symptomatic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) supplemented with physical therapy and exercises to targeted biological treatments. With regard to the latter, it was the advent of therapies targeting tumor necrosis factor-alpha (TNF-alpha) that actually revolutionized the field and raised the bar to an amount of response that is now considered as standard when new treatments beyond TNF blockade are being explored. Clinical trials with different anti-TNF agents have consistently shown important improvements in the signs and symptoms of patients with axial SpA (axSpA) in general and ankylosing spondylitis (AS) in particular [1–5]. A similar efficacy has been observed in the treatment of psoriatic arthritis (PsA), with TNF-blockers not only providing relevant relief of signs and symptoms but also slowing down the radiographic progression of erosions and joint space narrowing in peripheral arthritis of hands and feet [6–10].

Currently, four monoclonal antibodies (adalimumab, certolizumab, golimumab, and infliximab) and one TNF-receptor construct (etanercept) are globally indicated for the treatment of PsA and AS, with adalimumab, certolizumab, and etanercept currently also licensed in Europe for the treatment of the earlier manifestations of axial disease, currently referred to as non-radiographic axSpA (nr-axSpA). Despite the fact that no head-to-head trials are available, the clinical trial programs of all these biologicals have yielded remarkably similar results. In axSpA patients, the Assessment of SpondyloArthritis international Society (ASAS) responses were reached by approximately 60% of treated patients with regard to an improvement of 20% (ASAS20) and by 40% for the more stringent ASAS40 response. Moreover, in a

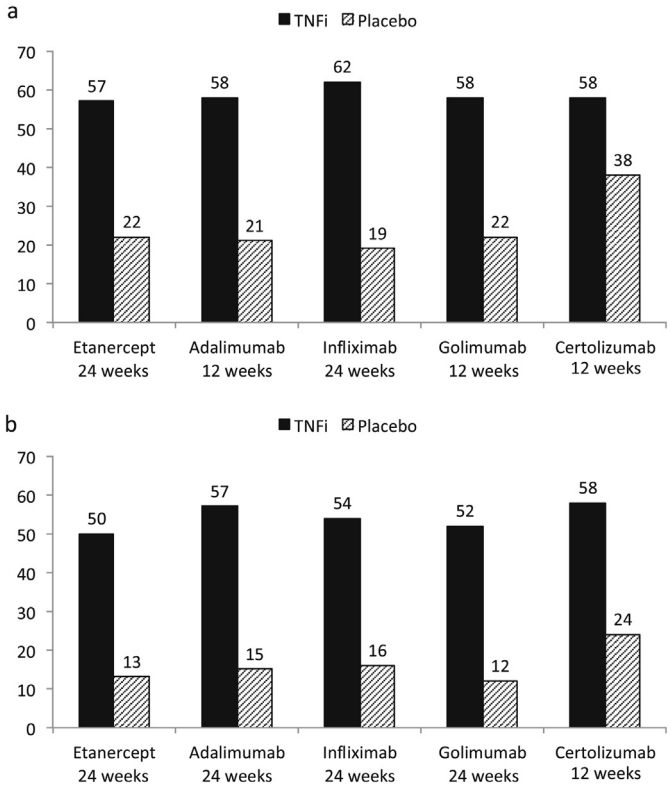


**Fig. 1.** a: ASAS20 responses in five separate trials in AS patients (*not* head to head) (results at 12–24 weeks). b: ACR20 responses in five separate trials in PsA patients (*not* head to head) (results at 12–24 weeks).