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The Future of Biological Therapies

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The last decade has witnessed a significant advance in the management of refractory moderate-to-severe psoriasis. This advance is the introduction of biological therapies to clinical practice. Three classes of biological therapies have been used. Of the first 2 classes to be introduced, the T-cell inhibitors and tumor necrosis factor (TNF)-α inhibitors, there have been differing fates with one of the T-cell inhibitors, efalizumab, being withdrawn because of a rare, unpredictable association with a usually fatal neurological condition, progressive multifocal leukoencephalopathy. In contrast, anti-TNF treatments are now firmly established offering a high level of efficacy and a good safety record across several indications, including psoriasis. A new approach involves targeting the p40 subunit, common to interleukins 12 and 23. Ustekinumab, the first drug in this class, now offers a viable alternative to anti-TNFs in the treatment of moderate-to-severe psoriasis. In this article, we discuss approaches that may be utilized to refine these existing therapies and examine future therapeutic targets for biological therapies.
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Biological therapies have revolutionized the treatment of moderate-to-severe psoriasis in the last decade. In particular, the introduction of the tumor necrosis factor (TNF)-α inhibitors for the treatment of psoriasis and psoriatic arthritis has been one of the most significant advances in psoriasis therapeutics in the last 30 years. Currently, adalimumab, etanercept, and infliximab are in widespread use with their role for the foreseeable future being in those patients who have tried and failed to benefit from, or are unsuitable for, other systemic agents and/or phototherapy.

The evolution of biological therapies has not been without problems, recently efalizumab, a T-cell inhibitor was withdrawn from the market[1] because of a rare (3 cases worldwide), unpredictable association with a usually fatal neurological condition, progressive multifocal leukoencephalopathy, all occurring in patients who had received the therapy for more than 3 years. In addition, there are concerns regarding increased rates of infection with all biological agents.[2] Specific side effects do occur, with reactivation of latent tuberculosis, demyelination, and worsening of heart failure being a concern with anti-TNFs.[2] Furthermore, there is significant variation in treatment response to biological therapies, especially in the case of psoriatic arthritis, such that 20%-50% of patients will derive little or no benefit while being exposed to potential toxicity. Thus, the quest for new and effective biological therapies and/or biomarkers of treatment response for existing biological therapies continues. In this article, we discuss methods that may be used to refine existing treatments and focus on new therapeutic targets, including interleukin (IL)-12/23, IL-17, and IL-22.

Refining Existing Therapies

An individual's genetic makeup can be critical to how they may respond to a given therapy. Genes encoding drug metabolizing enzymes, transporters, and drug targets may all be subject to functional polymorphisms and, overall, are estimated to account for 15%-30% of interindividual variation in drug response.[3] Pharmacogenetics[4] (the study of the relationship between individual gene variation and drug effect) offers the potential to identify individuals who may respond to a particular therapy and those at risk of adverse drug reactions before drug exposure.

With respect to biological agents, very little research has investigated the potential of pharmacogenetics to predict treatment response. Biological therapies are not metabolized to a great extent, thus it is likely that genetic variability in genes relevant to pharmacodynamic factors influence treatment response. There are at least 44 polymorphisms in the

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gene that encodes TNF.[5] One preliminary study, assessing some of these polymorphisms, has been carried out in 220 psoriasis patients treated with etanercept and 29 patients treated with adalimumab.[6] Patients self-evaluated their treatment using a visual analog scale (0-5). There was a moderate association between adalimumab responders and the TNF-1031 genotype (odds ratio = 4.43, $P = 0.04$). Further, larger studies have been performed in rheumatoid arthritis patients treated with anti-TNFs,[7,8] and a recent meta-analysis concluded that 1 variant, known as -308(A), appeared to predict poor response to TNF inhibitors.[9]

Interestingly, polymorphisms in the TNF, IL-12, and IL-23 pathways have all been shown to be risk factors for the development of psoriasis.[10] Thus, it is possible that response to anti-TNFs and IL-12/23 blockers in psoriasis may be influenced by psoriasis disease-susceptibility loci. In the future, genotype-phenotype correlation of the conditions currently included under the umbrella term "psoriasis" will be refined,[11] so too will the possibility of tailoring therapy to the individual patient. It is important to note that most pharmacogenetic studies performed in psoriasis therapeutics to date have been underpowered. Large-scale collaborative efforts are required to gain robust results and ultimately bring these techniques into everyday clinical practice.

There are new anti-TNF agents licensed for use in Crohn's disease and rheumatoid arthritis.[12,13] Certolizumab-pegol is unique because it consists of a Fab fragment of an anti-TNF antibody but lacks an antibody Fc domain.[13] Thus, it is devoid of any Fc receptor–mediated immune effector cell activities. Furthermore, certolizumab-pegol is, as the name suggests, pegylated so as to provide a longer serum half-life. The second new anti-TNF is golimumab. Like adalimumab, it is a fully human IgG1κ anti-TNF antibody.[14] Although these 2 biological therapies are of interest in the treatment of psoriasis and psoriatic arthritis, it is likely that future anti-TNFs will focus on improving the safety profile of this class of drugs. TNF-α exists in soluble (sTNF) and transmembrane (tmTNF) forms.[15] Recent work has demonstrated that sTNF (signaling primarily through TNFR1) and tmTNF (signaling through both TNFR1 and TNFR2) have different and sometimes opposing immunologic effects.[15] Furthermore, murine models have demonstrated that tmTNF is crucial in maintaining a normal innate immune response to infections, including listeria and tuberculosis, both important infections in the setting of anti-TNF therapy.[15] Thus, the development of biological drugs that are can effectively block only sTNF while sparing tmTNF may improve the safety profile of these agents with no loss of efficacy. Results from studies in murine models of inflammation and infection support this hypothesis and studies of biological therapies which work in this way are likely in the future.

Interleukins 12 and 23

A new class of biological drug targets the p40 subunit common to IL-12 and IL-23. These 2 cytokines, secreted by antigen-presenting cells, trigger differentiation of type 1 (T_h1) and type 17 (Th17) cells, both key effectors in the pathogenesis of psoriasis. Ustekinumab, the first in this new class of biological, is a fully human immunoglobulin G1κ monoclonal antibody, which binds to the shared p40 subunit of these cytokines with high affinity and specificity.

Two large phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel studies, PHOENIX 1 and PHOENIX 2, were performed to assess ustekinumab in the treatment of moderate-to-severe psoriasis.[16,17] In PHOENIX 1 study, 766 patients were randomized to receive 45 mg of ustekinumab (n = 255) or 90 mg of ustekinumab (n = 256) at weeks 0 and 4 and then every 12 weeks; or to receive placebo (n = 255) at weeks 0 and 4, with crossover to ustekinumab at week 12.[16] The primary endpoint, assessed by intention-to-treat analysis, was the percentage of patients achieving Psoriasis Area and Severity Index (PASI)-75 at week 12. At week 12, a total of 171 (67.1%) of the 45 mg dose group and 170 (66.4%) of the 90 mg group compared with 8 (3.1%) of the placebo group achieved PASI-75. PASI-90 was achieved in 106 (41.6%) and 94 (36.7%) of patients receiving 45 and 90 mg dose, respectively, compared with 5 (2%) of the placebo group. Those receiving placebo, achieved similar response rates after crossover to active treatment. The efficacy of ustekinumab continued to improve by week 24, with PASI-75 responses in 76.1% and 85% for the 45 and 90 mg ustekinumab groups, respectively. At week 40, long-term response had been achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group.

PHOENIX 2 trial showed similar week 12 PASI-75 response rates to those in PHOENIX 1 trial and also demonstrated that in partial responders who received dosing intensification of ustekinumab 90 mg every 12 weeks to ustekinumab 90 mg every 8 weeks, a significant increase was noted in those achieving PASI-75, compared with those who remained at a dose of ustekinumab 90 mg every 12 weeks, with response rates of 68.8% and 33.3%, respectively ($P = 0.004$).[17] There was no significant difference in response, however, in the patients randomized to receive 45 mg of ustekinumab every 8 weeks, compared with those who continued to receive 45 mg every 12 weeks.

The ACCEPT study, a single-blind randomized, parallel phase III study directly compared the safety and efficiency of ustekinumab and etanercept in treating 903 patients with psoriasis.[18] Patients were randomized to receive ustekinumab 45 or 90 mg at baseline and at week 4 or etanercept 50 g twice weekly for 12 weeks. At week 12 PASI-75 was achieved in 67.5% of those receiving 45 mg ustekinumab, 73.8% of those receiving 90 mg of ustekinumab, and 56.8% of those receiving etanercept.

Ustekinumab also has a role in the treatment of psoriatic arthritis. A randomized, double-blind, placebo-controlled, crossover phase 2 study was performed in 146 patients with psoriatic arthritis who had an inadequate response to disease-modifying antirheumatic drugs, non-steroidal anti-inflammatory drugs, or anti-TNF agents.[19] Patients received either 90 mg of subcutaneous ustekinumab per week for 4 weeks (group 1), followed by placebo at weeks 12 and 16, or placebo for 4 weeks, followed by 63 mg of subcutaneous ustekinumab at weeks 12 and 16 (group 2). The primary endpoint

was a 20% improvement from baseline in the American College of Rheumatology (ACR20) at week 12. Forty-two percent of patients in group 1 (ustekinumab-treated patients) achieved ACR20 at week 12 compared with 14% of those in group 2 (placebo-treated patients) ($P = 0.0002$). A phase III study is currently underway.

ABT-874

ABT-874 is a p40 monoclonal antibody, with a similar mechanism of action to ustekinumab. A phase 2 study of ABT-874, involving 180 patients, on 6 different dosing schedules demonstrated that after 12 weeks, PASI-75 was achieved in 63%-93% of patients, depending on dosing intensity.[20] Phase III studies are underway and are close to completion.

Interleukin 17

IL-17 is an inflammatory cytokine with numerous actions relevant to the pathogenesis of psoriasis. Recent studies have shown that IL-17 and IL-17–producing T cells may play an important role in psoriasis.[21] For example, IL-17 stimulates the production of inflammatory mediators and antimicrobial peptides that are commonly observed in plaques of psoriasis, and induces autocrine IL-22 production, leading to epidermal inflammation and acanthosis. Furthermore, IL-17 mRNA is elevated in psoriasis lesional tissue and decreases in response to therapy with either TNF-antagonist or ciclosporin.[22]

Two biological therapies, relevant to this pathway, have been studied: an IL-17 receptor antagonist and; one that directly targets IL-17. AMG 827 is a fully human IgG2 anti-IL-17 receptor monoclonal antibody, which selectively targets human IL-17R and antagonizes the IL-17 pathway. AIN457 is a recombinant high-affinity fully human monoclonal anti-human interleukin 17A antibody of the IgG1 class. AIN457 binds to human IL-17A and neutralizes the bioactivity of this cytokine. In a completed proof of concept study (CAIN457A2102), the effects of AIN457 administered at 3 mg/kg as a single intravenous infusion were compared with that of placebo in 36 patients with active chronic plaque psoriasis. The study demonstrated efficacy in the treatment of psoriasis with no safety events of concern being observed in this study.[23]

Interleukin 22

Accumulating evidence points to a role for IL-22 in the pathogenesis of psoriasis, with gene and/or protein expression of IL-22 and the IL-22 receptor being elevated both in psoriasis and murine models of skin inflammation.[24,25] IL-22 induces intracellular signal transduction via several transcription factors, including Jak 1, Tyk2, and JNK, ultimately affecting the gene expression of acute-phase reactants and antimicrobial peptides.[26] ILV-094 is a fully human IgG1γ antibody that binds potently to IL-22, thereby blocking its biological activity. It is being developed as a therapeutic agent for the treatment of both psoriasis and rheumatoid arthritis and is currently undergoing phase I trials, the results of which are expected in 2010.

Vascular Endothelial Growth Factor

One of the significantly under-researched histologic features of psoriasis is the presence of vascular angiogenesis driven in part by overexpression of vascular endothelial growth factor (VEGF) produced by keratinocytes,[27] despite this observation and that VEGF single nucleotide polymorphisms are associated with severe psoriasis of early onset.[28]

There has been no concerted investment in the use of anti-VEGF approaches for treatment of the disease. In contrast, VEGF antagonists have been developed for the treatment of colorectal cancer. The utility of this approach for psoriasis management is underscored by a case report of the use of bevacizumab (anti-VEGF) for the treatment of colon cancer in a psoriasis patient whose skin subsequently cleared.[29] Although this was not strictly serendipitous, there was prior art, it should be recognized that many therapies for psoriasis have developed because of serendipity and not from a reductionist, translational approach.

Conclusions

Biological therapies have revolutionized the treatment of moderate-to-severe psoriasis and the thinking behind it. Treatment goals are now more aggressive and long-term, toxicity-free therapies are realistic. However, technologies that can refine existing therapies and leverage off an increased understanding of the immunopathogenesis of psoriasis will ultimately lead to biological drugs that are still safer, more suited for long-term use and perhaps result in complete clearance of the disease.

References

1. EU: Wide recall of efalizumab (raptiva) Available at: http://www.emea.europa.eu Accessed: June 8, 2009
2. Menter A, Griffiths CE: Current and future management of psoriasis. Lancet 370:272-284, 2007
3. Eichelbaum M, Ingelman-Sundberg M, Evans WE: Pharmacogenomics and individualized drug therapy. Annu Rev Med 57:119-137, 2006
4. Vogel F: Moderne problem der humangenetik. Ergeb Inn Med Kinderheilkd 12:52-125, 1959
5. Nemec P, Pavkova-Goldbergova M, Stouracova M, et al: Polymorphism in the tumor necrosis factor-a gene promoter is associated with severity of rheumatoid arthritis in the Czech population. Clin Rheumatol 27: 59-65, 2008
6. Tejasvi T, Stuart P, Nair RP, et al: Preliminary pharmacogenetic assessment of tumor necrosis factor (TNF) polymorphisms in psoriasis: response to anti-TNF and systemic therapies. Br J Dermatol 159:1391, 2008
7. Seitz M, Wirthmuller U, Moller B, et al: The -308 tumour necrosis factor—gene polymorphism predicts therapeutic response to TNF—blockers in rheumatoid arthritis and spondyloarthritis patients. Rheumtology 46:93-96, 2007
8. Guis S, Balandraud N, Bouvenot J, et al: Influence of -308 A/G polymorphism in the tumor necrosis factor alpha gene on etanercept treatment in rheumatoid arthritis. Arthritis Rheum 57:1426-1430, 2007

9. O'Rielly DD, Roslin NM, Beyene J, et al: TNF-a -308 G/A polymorphism and responsiveness to TNF-a blockade therapy in moderate to severe rheumatoid arthritis: a systematic review and meta-analysis. Pharmacogenomics J 9:161-167, 2009
10. Nair RP, Duffin KC, Helms C, et al: Genome-wide scan reveals association of psoriasis with IL-23 and NF-$_k$B pathways. Nat Genet 41:199-204, 2009
11. Griffiths CE, Christophers E, Barker JN, et al: A classification of psoriasis vulgaris according to phenotype. Br J Dermatol 156:258-262, 2007
12. Choy EH, Hazleman B, Smith M, et al: Efficacy of a novel pegylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomized, dose-escalating trial. Rheumatology Oxford 41:1133-1137, 2002
13. Melmed GY, Targan SR, Yasothan U, et al: Certolizumab pegol. Nat Rev Drug Discov 7:641-642, 2008
14. Gladman D, Kavanaugh A, McInnes I, et al: Golimumab, a new human TNF-alpha antibody, administered every 4 weeks as a subcutaneous injection in psoriatic arthritis: nail, enthesitis, and dactylitis response in the randomized, placebo controlled, GO Reveal study. Ann Rheum Dis 67(suppl 2), 2008
15. Tracey D: Tumour necrosis factor alpha antagonist mechanism of action: a comprehensive review. Pharmacol Ther 117:244-279, 2008
16. Leonardi CL, Kimball AB, Papp KA, et al: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (Phoenix 1). Lancet 371:1665-1674, 2008
17. Papp KA, Langley RG, Lebwohl M, et al: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (Phoenix 2). Lancet 371:1675-1684, 2008
18. Griffiths CE, Strober B, van de Kerkhof PC, et al: A phase III, multicenter, randomized study comparing ustekinumab and etanercept for the treatment of moderate to severe plaque psoriasis. N Engl J Med 362:118-128, 2010
19. Gottlieb A, Menter A, Mendelsohn A, et al: Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet 373:633-640, 2009
20. Kimball AB, Gordon KB, Langley RG, et al: Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial. Arch Dermatol 144: 200-207, 2008
21. Lowes MA, Kikuchi T, Fuentes-Duculan J, et al: Psoriasis vulgaris lesions contain discrete populations of T_h1 and Th17 T cells. J Invest Dermatol 128:1207-1211, 2008
22. Haider AS, Lowes MA, Suárez-Fariñas M, et al: Identification of cellular pathways of "type 1," Th17 T cells, and TNF- and inducible nitric oxide synthase-producing dendritic cells in autoimmune inflammation through pharmacogenomic study of cyclosporine A in psoriasis. J Immunol 180:1913-1920, 2008
23. A Study Comparing AIN457 to Placebo in Subjects with a Diagnosis of Moderate to Severe Stable Plaque Psoriasis available at: http://clinicaltrials.gov
24. Wolk K, Witte E: IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. Eur J Immunol 36:1309-1323, 2006
25. Zheng Y, Danilenko P, Vadez I, et al: Interleukin-22, a T_H17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. Nature 445:648-651, 2007
26. Dumoutier L, Louahed J: Human interleukin 10 related T cell derived inducible factor: molecular cloning and functional characterization as an hepatocyte stimulating factor. Proc Natl Acad Sci USA 97:10144-10149, 2000
27. Detmar M, Brown LF, Clattery KP, et al: Over expression of vascular permeability factor/vascular endothelial growth factor and its receptor in psoriasis. J Exp Med 180:1141-1146, 1994
28. Young HS, Summers AM, Bhushan M, et al: Single nucleotide polymorphism of vascular endothelial growth factor in psoriasis of early onset. J Invest Dermatol 122:209-211, 2004
29. Akman A, Yilmaz E, Mutlu H, et al: Complete remission of psoriasis following bevacizumab therapy for colon cancer. Clin Exp Dermatol 34:e202-e204, 2009