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Use of TNF blockers and other targeted therapies in rare refractory immune-mediated inflammatory diseases: evidence-based or rational?

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ABSTRACT

Evidence-based medicine implies that clinical decision making should be based on external research evidence when available. This external evidence includes, but is certainly not restricted to, randomised controlled trials (RCTs). The development of powerful but often expensive targeted therapies for immune-mediated inflammatory diseases (IMIDs) is one of the major successes of evidence-based medicine but, paradoxically, also threatens the traditional RCT-based approach. Indeed, the increasing availability of these drugs decreases the number of patients available for RCTs, questions the ethical basis for the use of placebo groups and raises the issue of cost-efficacy. These considerations become even more important in rare phenotypically diverse and potentially life- or organ-threatening IMIDs such as sarcoidosis, Behçet's disease and uveitis. Using the successful application of tumour necrosis factor blockade in these diseases as an example, this review defends the concept that pathophysiological insights in cellular and molecular disease pathways as well as limited case series are valid sources of external evidence for the rational use of targeted therapies in these rare refractory conditions. If authors fail to redefine their concept of rational therapy along the lines of not only evidence-based but also pathophysiology-based and practice-based medicine, they may underestimate the potential of novel drugs in rare refractory IMIDs and thereby jeopardise the health of their patients.

CONCEPT OF RATIONAL THERAPY: EVIDENCE-BASED MEDICINE

Over the last two decades the practice of medical care has shifted from eminence-based medicine (ironically defined as repeating the same mistakes with increasing confidence) towards evidence-based medicine.[1] This concept implies that medical decision making in an individual patient should be based on or tested against external research evidence where available[2]: all medical interventions in general—and pharmacological treatments in particular—should ideally have 'proven' efficacy and safety. Although not the only source of valid evidence, prospective, randomised, double-blind, placebo controlled trials are generally considered to be the gold standard to demonstrate efficacy of pharmacological treatment.[3] [4] In combination with meta-analyses and large-scale observational studies,[5] these trials also provide the basis for objective assessment of safety. Although translation from evidence to practice remains challenging,[6–8] the implementation of evidence-based medicine

has proved extremely useful in many medical subdisciplines.

Paradoxically, the immense success of new treatment strategies along the principles of evidence-based medicine starts to challenge the concept itself. First, regulatory authorities and insurance companies are adding cost-efficacy as a new outcome in addition to efficacy and safety in order to control the economic consequences of the availability of potent but often very expensive new drugs. Second, the increasing pace of new drug development makes it more and more difficult to enrol sufficient numbers of patients in clinical trials, especially when studying rare and phenotypically heterogeneous diseases. Finally, the availability of these potent novel drugs questions the medical as well as the ethical grounds to use the classical controlled study design in severe conditions with short-term mortality or irreversible morbidity. In this review we discuss how these three factors may jeopardise the use of highly effective targeted therapies in severe immune-mediated inflammatory diseases if we fail to redefine the principles of rational therapy beyond the limits of classical 'evidence' coming from randomised placebo controlled studies.

IMMUNE-MEDIATED INFLAMMATORY DISEASES

Immune-mediated inflammatory diseases (IMIDs) are a novel conceptual framework regrouping diseases where anatomical and functional damage of organ systems and the resulting morbidity is primarily caused by immune-driven inflammation. This concept is a counterpart of disease entities such as oncology, regrouping all human diseases primarily caused by malignant transformation, and infectious diseases, defined as disorders with bacteria, viruses, fungi or parasites as primary aetiological agents. Although immune cells and inflammation are also pivotal players in oncology and infectious diseases, they are the primary causal factor rather than a secondary mechanism in IMIDs. Thus, IMIDs encompasses many forms of autoimmunity (inflammatory bowel disease (IBD), psoriasis, multiple sclerosis, rheumatoid arthritis, autoimmune vasculitis, systemic lupus erythematosus, etc) as well as solid graft rejection, graft versus host disease, autoinflammatory syndromes, asthma, atherosclerosis and inflammatory disorders of unknown origin such as IBD, sarcoidosis and Behçet's disease (BD).

Regrouping these diseases under the common denominator of IMIDs has two major advantages. First, it promotes a pathogenic rather than

phenotypic disease classification reflecting the emerging knowledge that similar immunological disease mechanisms can affect different organs (such as gut and joint inflammation in spondyloarthritis (SpA)) and that different diseases can share similar organ involvement (such as gut inflammation in Crohn's disease and SpA).[9] This new perspective facilitates the translation from new therapeutic concepts from one disease entity to another, as illustrated by the introduction of tumour necrosis factor (TNF) blockade for SpA based on the efficacy in Crohn's disease.[10] Second, it provides a conceptual framework to investigate the disease-specific versus common pathways of inflammation between different diseases as well as between different types of organ involvement within one disease.[11] As a prototypical example, recent genetic and molecular insights have identified the pyrin-cryopyrin-interleukin 1 pathway as a central player in a number of rare but severe systemic autoinflammatory syndromes.[12–16] The mechanistic insights in this shared inflammatory pathway have led to the successful use of interleukin 1 (IL-1) blockade for these diseases.[17] [18] Other diseases in which the same pathway is affected, such as gout,[19] also turned out to be responsive to IL-1 blockade.[20]

Fibrosis is another prototypical example of a common downstream pathway which is one of the main causes of irreversible anatomical and functional organ damage in many IMIDs. Early observations of antifibrotic effects of imatinib mesylate, a tyrosine kinase inhibitor, in chronic myelogenous leukaemia[21] has led to a rapid exploration of the potential of this new drug in other fibrotic conditions in experimental models[22–25] as well as in severe IMIDs in humans.[26–29]

Most importantly, however, targeted therapeutic interventions also taught us that not all cellular and molecular pathways of inflammation are 'public', but that some pathways are specific for a distinct IMID. As an example, B cell depletion is a proven effective treatment for rheumatoid arthritis but does not seem to have a major impact on SpA, the second most common form of chronic inflammatory arthritis.[30] Even more striking, some pathways appear to play a role in one type of organ involvement but not in others within one single IMID. This is best illustrated by the efficacy of T cell-targeted therapies such as efalizumab (anti-LFA-1) and alefacept (LFA-3/IgG1 fusion protein) for skin involvement in psoriasis but not for joint inflammation in psoriatic arthritis.[31–34]

Taken together, these examples indicate that the concept of IMIDs does not mean that all targeted anti-inflammatory therapies should per se be considered in all conditions, but illustrate how a better understanding of disease-specific pathophysiological mechanisms and common pathways shared across different inflammatory conditions favours a rational rather than purely empirical use of targeted therapies.

MECHANISM-BASED MEDICINE IN RARE IMIDs
The identification of key cellular and molecular pathways in IMIDs in combination with our ability to specifically modulate them in vivo by targeted therapies has profoundly changed our approach to human immunology and inflammation. From a clinical perspective, this evolution raises the question whether mechanistic insights in the pathophysiology of a disorder should be considered as an additional piece of external evidence in clinical decision making and should thus become an integral part of evidence-based medicine. Obviously, classical evidence-based medicine is still the preferred approach for most common IMIDs. However, some of these diseases share three features which preclude large placebo controlled trials and therefore favour mechanistic considerations. First, diseases

such as Takayasu's vasculitis or eosinophilic fasciitis are too rare to recruit sufficient numbers of patients for prospective randomised controlled trials. The scarcity of study patients is further increased by the fact that the use of novel treatments is mainly restricted to those patients failing standard treatment. Second, slightly more common IMIDs such as sarcoidosis or systemic lupus erythematosus have an important phenotypic diversity. This phenotypic diversity complicates the definition of global outcome parameters and the randomisation in clinical trial design. Finally, the severity of these disorders may lead to irreversible organ damage in the short term, as illustrated by visual impairment in refractory autoimmune uveitis, and thus hampers the use of a randomised controlled study design to prove the efficacy of novel treatments.

The relative scarcity of hard evidence for efficacy from randomised controlled trials (RCTs) in these rare, severe and treatment-resistant diseases should, however, be balanced against the two other aspects of rational therapy—safety and cost-efficacy. Most of the novel drugs which could be used in these rare indications have already been extensively tested and validated in more common immune-mediated inflammatory disorders, leading to extensive data on safety and potential side effects. As to cost-efficacy, the relatively high cost of most novel targeted therapies should be considered in the context of the low absolute number of patients with refractory disease as well as the extremely high human and financial costs of severe morbidity resulting from insufficient treatment in these conditions. Considering the mechanistic insights in the underlying disease pathways, the clinical severity and potential morbidity of these rare IMIDs and the efficacy and safety profile of novel targeted therapies in related conditions, one can wonder if it is not irrational rather than rational to require RCTs as hard evidence in these conditions.

The issues raised here about how one should define rational therapy in rare treatment-resistant IMIDs are best illustrated by the increasing use of TNF blockade in these conditions. We will discuss here in some more detail the use of TNF blockers in severe and treatment-resistant sarcoidosis, BD and refractory uveitis to illustrate how low prevalence and severe morbidity can urge physicians to use other standards for rational therapy.

TNF BLOCKADE IN SEVERE REFRACTORY SARCOIDOSIS
Sarcoidosis is a systemic granulomatous disorder of unknown origin. The disease affects all racial and ethnic groups and occurs at all ages with an incidence peaking in the third decade.[35] The incidence of sarcoidosis varies widely throughout the world, with the highest incidence of 0.05–0.4 per 1000 patient-years in northern European countries.[36] Although lung involvement is the most common manifestations of sarcoidosis, the clinical presentation can be clinically extremely heterogeneous with potential involvement of all organs (skin, eyes, bone, internal organs). Persistent morbidity can result from the progression of inflammation towards fibrosis with subsequently irreversible organ damage. Depending on the severity and the target organ, the recommended therapy for sarcoidosis differs from none to a combination of immunosuppressive drugs.[37] The heterogeneous presentation, the variable course of the disease (from spontaneous remission to irreversible organ loss) and the lack of internationally accepted and validated disease activity scores hampers the systematic study of homogenous patient groups.

TNF blockade has been explored for the treatment of severe refractory sarcoidosis as granuloma formation is regulated by a complex interaction between T lymphocytes and macrophages in which cytokines such as TNF play a central role.[36] As lung

sarcoidosis is the most common form of the disease, a phase II multicentre randomised double-blind placebo controlled study of infliximab was conducted in 138 patients with chronic sarcoidosis with pulmonary involvement.[38] Patients in the combined infliximab groups (3 and 5 mg/kg) had a statistically significant improvement in percentage predicted forced vital capacity (FVC) (mean increase of 2.5% from baseline to week 24) compared with no change in placebo-treated patients (p=0.038). In the same study, there was also a beneficial effect on extrapulmonary sarcoidosis.[39] Although a smaller RCT failed to achieve statistically significant improvement in lung function,[40] nine case series with a total of 50 patients reported a positive treatment outcome with infliximab in different types of sarcoidosis, including eye and central nervous system involvement (table 1). In contrast, the soluble TNF receptor etanercept failed to show therapeutic efficacy in both an open-label trial in acute pulmonary sarcoidosis and a randomised placebo controlled trial in methotrexate-resistant chronic ocular sarcoidosis.[41 42] Although not formally proven, it is conceivable that the soluble receptors and monoclonal antibodies targeting TNF have some differential effects in granulomatous diseases such as sarcoidosis, Crohn's disease or tuberculosis, eventually resulting in slightly different efficacy or safety profiles. This again emphasises the fact that detailed insights in the pathophysiological pathways and mechanisms of action are required for the optimal use of these drugs in specific cases. Whereas the main message remains that we need additional RCTs to confirm the efficacy of TNF blockers in different types of sarcoidosis and to assess potential differences between the different drugs, these studies (as well as multiple single case reports) provide a strong medical and ethical rationale for the use of TNF blockade in refractory cases with direct organ treat.

TNF BLOCKADE IN SEVERE REFRACTORY BD

BD is a multisystem chronic and relapsing inflammatory disorder of unknown aetiology which is often considered as a complex systemic vasculitis with neutrophilic and lymphohistiocytic inflammation. Whereas the prevalence can reach 0.1–0.4% in some regions of the Middle East, the Far East and the Mediterranean region, the prevalence in Western countries is only 2 per 100 000.[43] The disease starts with recurrent mucocutaneous lesions in 80% of patients. Although painful and debilitating, these lesions are relatively benign and can be treated with local therapy or classical drugs such as colchicine. Besides the characteristic mucocutaneous and rheumatological symptoms, patients may develop ocular, gastrointestinal, vascular and/or central nervous system inflammation.[44] These manifestations require acute and aggressive treatment as they may ultimately result in organ- and/or life-threatening situations in the small subset of patients refractory to aggressive immunosuppressive treatment or those developing unacceptable side effects.

Although the exact aetiology of BD remains obscure, the elevated TNF expression in active uveitis and in oral ulcers of patients with BD has provided a theoretical rationale for the use of TNF blockade in severe refractory BD.[45] The clinical efficacy of TNF blockade has been confirmed in a randomised trial of the soluble TNF receptor etanercept in mucocutaneous BD.[46] However, the low incidence and acute severity of the disease hampers RCTs in refractory ocular, vascular or central nervous system BD. Despite this lack of 'hard' evidence, nine open prospective studies with a total of 103 treated patients and 21 case series with a total of 106 patients strongly support the potential therapeutic efficacy of the different TNF blockers in severe organ- and/or life-threatening refractory BD (table 2).

TNF BLOCKADE IN SEVERE REFRACTORY UVEITIS

Inflammation of the uvea, the pigmented middle of the three concentric layers in the eye, is generally classified anatomically as anterior uveitis, pars planitis (affecting the part of the eye just between the retina and the ciliary body) and posterior uveitis. The global incidence of uveitis is 0.5 per 1000 person-years. Posterior uveitis, however, accounts for only 10% of the cases presenting to the ophthalmologist, reaching only 0.05 per 1000 person-years.[47] In contrast to the phenotypic diversity of sarcoidosis and BD manifestations, the major issue with severe uveitis is the multitude of possible aetiologies. Indeed, pathophysiological classifications distinguish granulomatous from non-granulomatous uveitis, infectious uveitis and uveitis in the context of systemic inflammatory diseases such as SpA, IBD, juvenile idiopathic arthritis and the previously discussed BD and sarcoidosis. Approximately 30% of cases of uveitis do not fit into any apparent aetiological category and are therefore classified as idiopathic uveitis. As for most IMIDs, the majority of cases respond well to conventional therapy including local glucocorticosteroids and systemic immunosuppressive drugs.

Table 1 Overview of randomised controlled trials (RCTs), open prospective trials and case series on the use of TNF blockade in sarcoidosis

RCTs	Open trials	Case series	Outcome	Drug	References
n=93			Positive	IFX	Baughman et al[36]
n=93			Positive	IFX	Judson et al[39]
n=13			Mixed	IFX	Rossman et al[40]
n=9			Negative	ETN	Baughman et al[42]
	n=17		Negative	ETN	Utz et al[41]
		n=12	Positive	IFX	Saleh S. *Respir Med* 2006;**100**:2053–59.
		n=9	Positive	IFX	Sweiss N. *Arthritis Rheum* 2005;**53**:788–91.
		n=7	Positive	IFX	Baughman RP. *Int J Clin Pharmacol Ther* 2005;**43**:7–11.
		n=7	Positive	IFX	Moravan M. *Neurology* 2009;**72**:337–40.
		n=5	Positive	IFX	Pritchard C. *Ann Rheum Dis* 2004;**33**:318–20.
		n=3	Positive	IFX	Baughman RP. *Sarcoidosis Vasc Diffuse Lung Dis* 2001;**18**:70–4.
		n=3	Positive	IFX	Murphy C. *Ophthalmology* 2004;**111**:352–6.
		n=2	Positive	IFX	Cruz B. *Rheumatol Int* 2007;**27**:1181–3.
		n=2	Positive	IFX	Katz JM. *Arch Neurol* 2003;**60**:426–30.

Single case reports are not included in the list of references.
The number of patients exposed to the TNF blocker is shown and the outcome of the treatment is scored as positive, mixed or negative according to the conclusion of the authors of the referenced manuscripts.
ETN, etanercept; IFX, infliximab; TNF, tumour necrosis factor.

Table 2 Overview of randomised controlled trials (RCTs), open prospective trials and case series on the use of TNF blockade in Behçet's disease

RCTs	Open trial	Case series	Outcome	Drug	References
n=20			Positive	ETN	Melikoglu et al[46]
	n=25		Positive	IFX	Sfikakis PP. *Ann Intern Med* 2004;**140**:404–6.
	n=13		Positive	IFX	Ohno S. *J Rheumatol* 2004;**31**:1362–8.
	n=13		Positive	IFX	Tugal-Tutkun I. *Arthritis Rheum* 2005;**52**:2478–84.
	n=12		Positive	IFX	Niccoli L. *Rheumatology* 2007;**46**:1161–4.
	n=12		Positive	IFX	Accorinti M. *Jpn J Ophthalmol* 2007;**51**:191–6.
	n=10		Positive	IFX	Al-Rayes H. *Rheumatol Int* 2008;**29**:53–7.
	n=7		Positive	IFX	Tognon S. *Ann NY Acad Sci* 2007;**1110**:474–84.
	n=6		Positive	IFX	Abu El-Asrar AM. *Int Ophthalmol* 2005;**26**:83–92.
	n=5		Positive	IFX	Kikuchi H. *J Neurol Sci* 2008;**272**:99–105.
		n=20	Positive	IFX	Tugal-Tutkun I. *J AAPOS* 2008;**12**:611–13.
		n=13	Positive	IFX	Nakamura S. *Int Ophthalmol Clin* 2005;**45**:179–89.
		n=10	Positive	IFX	Tabbara K. *Am J Ophthalmol* 2008;**146**:845–50.
		n=8	Positive	IFX	Pipitone N. *Arthritis Rheum* 2008;**59**:285–90.
		n=6	Positive	IFX	Lindstedt EW. *Br J Ophthalomol* 2005;**89**:533–6.
		n=6	Positive	IFX	Naganuma M. *Inflamm Bowel Dis* 2008;**14**:1259–64.
		n=5	Positive	IFX	Sfikakis PP. *Lancet* 2001;**358**:295–6.
		n=5	Positive	IFX	Arayssi T. *Clin Exp Rheumatol* 2005;**23**:427.
		n=4	Positive	IFX	Bodaghi B. *Ann Rheum Dis* 2005;**64**:962–4.
		n=4	Mixed	IFX	Lanthier N. *Presse Med* 2005;**34**:916–18.
		n=3	Positive	ADL	Mushtaq B. *Eye* 2007;**21**:824–5.
		n=3	Positive	ADL	van Laar JA. *Ann Rheum Dis* 2007;**66**:565–6.
		n=3	Positive	ETN, IFX	Aeberli D. *Swiss Med Wkly* 2002;**132**:414–22.
		n=3	Negative	IFX	Seyahi E. *Rheumatology* 2007;**46**:1213–14.
		n=3	Positive	IFX	Joseph A. *Ophthalmology* 2003;**110**:1449–53.
		n=2	Positive	IFX, ETN, ADL	van Laar JA. *Ned Tijdschr Geneeskd* 2006;**150**:705–9.
		n=2	Positive	IFX	Katsiari C. *Adv Exp Med Biol* 2003;**528**:551–5.
		n=2	Negative	IFX	Yücel AE. *Rheumatology* 2004;**43**:394–6.
		n=2	Positive	IFX	Travis SP. *Gut* 2001;**49**:725–8.
		n=2	Positive	IFX	Mansour A. *Ophthalmology* 2004;**111**:197–8.

Single case reports are not included in the list of references.
The number of patients exposed to the TNF blocker is shown and the outcome of the treatment is scored as positive, mixed or negative according to the conclusion of the authors of the referenced manuscripts.
ADL, adalimumab; ETN, etanercept; IFX, infliximab; TNF, tumour necrosis factor.

The major issue is the direct threat of irreversible loss of sight and related medical, social and professional handicap in case of treatment-refractory disease.

Although the pathophysiology of uveitis may be very diverse with regard to the exact aetiology, there is ample evidence that TNF blockade is effective for systemic inflammatory diseases such as SpA and IBD which are associated with uveitis. Data from trials in these diseases suggest that TNF blockade is also effective for the ocular manifestations, but these trials are obviously underpowered to assess this stringently as the incidence of uveitis remains low in these conditions.[48] On the other hand, the aetiological diversity and the potential risk of deterioration of underlying infectious or demyelinising conditions hampers RCTs of TNF blockade in uveitis across different IMIDs. Reviewing the published evidence, the only two randomised placebo controlled trials were conducted with the soluble TNF receptor etanercept and failed to show significant benefit,[49] [50] even though two open prospective studies with etanercept did show beneficial effects.[51] [52] This discrepancy may relate to the type of uveitis, the small number of patients included, as well as the reliability and validity of the outcome parameters, highlighting the previously discussed issues in trials in this type of rare and heterogeneous condition. In contrast, 14 open prospective studies with a total of 173 patients and 26 case series with a total of 344 patients did show unequivocal therapeutic efficacy of the anti-TNF monoclonal antibodies infliximab and adalimumab for severe refractory uveitis (table 3). Whereas potential differences in efficacy between the soluble receptors and the monoclonal antibodies remain to be systematically investigated, these data provide ample evidence for the rational use of anti-TNF agents in sight-threatening refractory uveitis.

PRACTICE-BASED MEDICINE

The experience with TNF blockade in severe and refractory sarcoidosis, BD and uveitis illustrates well that, even in the absence of data from RCTs, novel targeted treatments can not only be rational but even medically and ethically inevitable in selected cases with severe IMIDs. Accordingly, the Dutch authorities have approved reimbursement of several TNF blockers for these indications even in the absence of official registration. It needs, however, to be clearly emphasised that this should not be misinterpreted as a recommendation to use TNF blockers in these conditions. The knowledge on the efficacy and safety of these drugs in these conditions is still limited and may be severally biased by the fact that successful cases are more easily reported than failures. The sole purpose of these three examples is to illustrate that there is a genuine issue here which, partially due to local legal and financial considerations, may lead to important differences in medical practice. It is also obvious that, although we have used examples related to TNF blockade, the same issues pertain to the use of IL-1 blockade in fever syndromes and Still's disease, the use of B cell-directed biological agents in autoantibody-associated conditions such as antineutrophil cytoplasmic antibody-associated vasculitis and even the use of nonbiological targeted therapies such as the previously mentioned tyrosine kinase inhibitors in fibrotic conditions. Accordingly, the

Table 3 Overview of randomised controlled trials (RCTs), open prospective trials and case series on the use of TNF blockade in refractory uveitis

RCTs	Open trials	Case series	Outcome	Drug	References
n=10			Negative	ETN	Foster et al[49]
n=7			Negative	ETN	Smith et al[50]
	n=25		Positive	IFX	Sfikakis PP. *Ann Intern Med*. 2004;**140**:404–6.
	n=23		Positive	IFX	Suhler E. *Arch Ophthalmol* 2005;**123**:903–12.
	n=19		Positive	ADL	Diaz-Llopis M. *J Ocul Phramacol Ther* 2008;**24**:351–61.
	n=17		Positive	ETN	Murphy et al[51]
	n=14		Positive	ADL	Vazquez-Cobian LB. *J Pediatr* 2006;**149**:572–5.
	n=13		Positive	IFX	*Ohno S. *J Rheumatol* 2004;**31**:1362–8.
	n=13		Positive	IFX	*Tugal-Tutkun I. *Arthritis Rheum* 2005;**52**:2478–84.
	n=12		Positive	IFX	*Accorinti M. *Jpn J Ophthalmol* 2007;**51**:191–6.
	n=11		Mixed	IFX	Simonini G. *Rheumatology* 2008;**47**:1510–14.
	n=10		Positive	ETN	Reiff et al[52]
	n=10		Positive	IFX	*Al-Rayes H. *Rheumatol Int* 2008;**29**:53–7.
	n=10		Positive	IFX	Markomichelakis NN. *Am J Ophthalomol* 2004;**138**:648–50.
	n=7		Positive	IFX	*Tognon S. *Ann NY Acad Sci* 2007;**1110**:474–84.
	n=7		Positive	IFX	Benitez-del-Castillo JM. *Eye* 2005;**19**:841–5.
	n=6		Positive	IFX	*Abu El-Asrar AM. *Int Ophthalmol* 2005;**26**:83–92.
	n=3		Positive	IFX	El-Shabrawi Y. *Arthritis Rheum* 2002;**46**:2821–4.
		n=47	Mixed	ADL, ETN, IFX	Foeldvari I. *J Rheumatol* 2007;**34**:1146–50.
		n=46	Mixed	ADL, ETN, IFX	Guignard S. *Ann Rheum Dis* 2006;**65**:1631–4.
		n=27	Positive	IFX	Sobrin L. *Arch Ophthalmol* 2007;**125**:895–900.
		n=24	Mixed	ETN, IFX	Saurenmann RK. *Rheumatology* 2006;**45**:982–9.
		n=20	Mixed	ADL	Tynjälä P. *Rheumatology* 2008;**47**:339–44.
		n=20	Positive	IFX	*Tugal-Tutkun I. *J AAPOS* 2008;**12**:611–13.
		n=18	Positive	ADL	Biester S. *Br J Ophthalmol* 2007;**91**:319–24.
		n=18	Positive	ADL, IFX	Gallagher M. *Br J Ophthalmol* 2007;**91**:1341–4.
		n=17	Positive	IFX	Kahn P. *Ophthalmology* 2006;**113**:860–4.
		n=16	Positive	IFX	Ardoin S. *Am J Ophthalomol* 2007;**144**:844–9.
		n=13	Positive	IFX	*Lindstedt EW. *Br J Ophthalomol* 2005;**89**:533–6.
		n=12	Positive	IFX	*Bodaghi B. *Ann Rheum Dis* 2005;**64**:962–4.
		n=10	Positive	ADL	Callejas-Rubio JL. *J Ocul Pharmacol Ther* 2008;**24**:613–14.
		n=6	Positive	IFX	Sharma S. *Ann Rheum Dis* 2007;**66**:840–1.
		n=6	Positive	IFX	Richards J. *Clin Exp Ophthalomol* 2005;**33**:461–8.
		n=6	Positive	IFX	Rajaraman R. *Ophthalmology* 2006;**113**:308–14.
		n=5	Mixed	ADL, IFX	Huynh N. *Ocul Immunol Inflamm* 2008;**16**:89–93.
		n=5	Positive	IFX	*Sfikakis PP. *Lancet* 2001;**358**:295–6.
		n=5	Positive	IFX	*Arayssi T. *Clin Exp Rheumatol* 2005;**23**:427.
		n=5	Positive	IFX	*Joseph A. *Ophtalmology* 2003;**110**:1449–53.
		n=4	Mixed	ETN, IFX	Coates LC. *Ann Rheum Dis* 2008;**67**:729–30.
		n=4	Mixed	IFX	*Lanthier N. *Presse Med* 2005;**34**:916–18.
		n=3	Positive	ADL, IFN	Sebastian RT. *Arch Ophthalmol* 2006;**124**:1505.
		n=3	Positive	ADL	*Mushtaq B. *Eye* 2007;**21**:824–25.
		n=2	Positive	IFX	Rispo A. *Scand J Rheumatol* 2005;**34**:387–91.
		n=2	Mixed	ETN, IFX	Milman N. *APMIS* 2006;**114**:912–19.

Single case reports are not included in the list of references.
The number of patients exposed to the TNF blocker is shown and the outcome of the treatment is scored as positive, mixed or negative according to the conclusion of the authors of the referenced manuscripts.
*These studies also appear in table 2 as all or some of the patients had uveitis in the context of Behçet's disease.
ADL, adalimumab; ETN, etanercept; IFX, infliximab; TNF, tumour necrosis factor.

key question is not which treatment should be recommended for which conditions but, more generically, how the medical community can structurally translate and integrate this new evolution in daily practice.

First, it is obvious that, even in these rare and severe conditions, the medical community must aim for controlled trials. As rare and severe diseases may be less attractive for pharmaceutical companies, it is clear that there is a specific place here for investigator-initiated trials which should ideally be supported by local authorities and/or international organisations in the context of orphan disease and/or drug programmes. Innovative trial design can help to overcome some of the specific hurdles in these conditions. For example, severe conditions may require an open label treatment followed by a controlled and blinded tapering of the experimental drug using time-to-relapse as outcome

parameter and including early escape possibilities. This type of trial is already commonly used and recognised in paediatrics.[53 54] Alternatively, as corticosteroids remain the corner stone of the treatment of most if not all severe IMIDs but often lead to unacceptable long-term side effects, the tapering of corticosteroids may be used as one of the primary outcome parameters in these conditions. Besides an alternative trial design, the inclusion of key biomarkers related to the inflammation pathway targeted by the treatment as outcome parameter may help to reduce the size and duration of clinical trials, especially when the clinical outcome of the treatment is long-term preservation of organ function and anatomical integrity. One example is the use of biomarkers for cartilage and bone degradation and remodelling in arthritis as it is ethically and medically unacceptable to wait until irreversible damage can be measured by classical imaging

methods. Finally, consensus statements and recommendations by international expert panels should aim to frame innovative treatments in rare conditions until controlled trials have been conducted. These position papers can either focus on the potential indications for targeted treatments[55] or discuss the management of specific conditions.[56]

Second, this issue should be considered in the current trend towards personalised medicine. Even when data are available from randomised placebo controlled trials, they provide information on the efficacy and safety (and eventually cost-efficacy) of a drug at the group level but not at the individual level. Thus, this 'evidence' of efficacy is merely a statistical notion reflecting the significantly higher chance of a single patient having a satisfactory clinical response to a given drug in comparison with placebo or a standard drug, rather than evidence that a single patient will indeed benefit from that 'proven' intervention. When translated to medical practice, this means that a physician will use this external information to compare the chances of success of different treatment options for his/her patients and to decide whether or not to start the treatment. At the end, however, the physician will monitor the single patient and evaluate the individual effects and side effects to decide if it is rational or not to give this treatment to the patient. Accordingly, even for drugs which have been extensively evaluated in clinical trials, the clinical response of a single patient remains the gold standard for rational therapy. Whereas the aim of personalised medicine is to develop tools to further increase our chances of success in individual patients according to their genetic, biological or phenotypic profile, we still perform 'experimental' medicine in each of our patients. These considerations equally apply to novel non-approved treatments for rare refractory IMIDs: whereas the a priori information on the exact chances of a patient to benefit from the treatment is weaker than for registered treatments, the fundamental principles of rational therapy remain that the chance of benefit should be balanced against the risk of not treating the patient and that the individual response is, in the end, the gold standard.

Finally, these considerations certainly do not plead for uncontrolled prescription of non-registered drugs for rare indications. On the contrary, they emphasise the need to restructure and organise the use of these treatments in non-approved indications. Until properly conducted RCTs become available, the use of novel targeted treatments for non-registered indications should probably be considered exclusively in patients with rare conditions who are refractory to all standard treatment protocols and in whom severe morbidity and/or mortality are expected in the short term. Moreover, expert advice, standardised treatment, careful follow-up for objective individual improvement and mandatory registration with open source access all seem logical measures in order to reconcile maximal benefit for the patient with optimal collection and sharing of evolving medical knowledge. If we fail to redefine our concept of evidence and rational therapy along these lines, we may underestimate the potential of novel drugs in rare refractory IMIDs and thereby jeopardise the health of our patients.

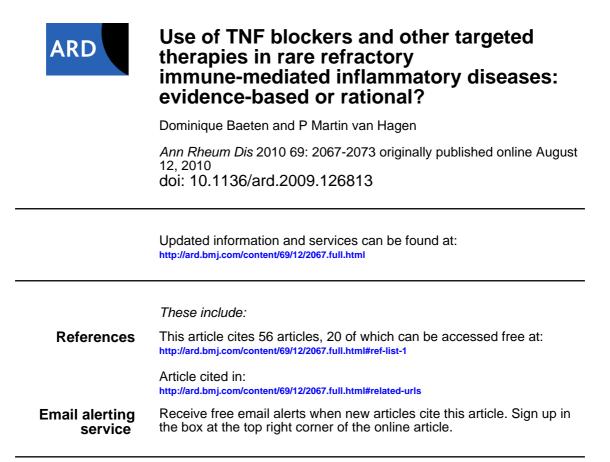## REFERENCES

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