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

Dominique Baeten,¹ P Martin van Hagen²

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: 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 ⁷ 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 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 knowl-
edge that similar immunological disease mechanisms can affect
different organs (such as gut and joint inflammation in spon-
dyloarthropathy (SpA)) and that different diseases can share similar
organ involvement (such as gut inflammation in Crohn’s disease
and SpA). 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.
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. 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 syn-
dromes. The mechanistic insights in this shared inflamma-
tory pathway have led to the successful use of interleukin 1
(IL-1) blockade for these diseases. Other diseases in which
the same pathway is affected, such as gout, also turned out to
be responsive to IL-1 blockade.

Fibrosis is another prototypical example of a common down-
stream pathway which is one of the main causes of irrevers-
able anatomical and functional organ damage in many IMIDs.
Early observations of antifibrotic effects of imatinib mesylate, a
tyrosine kinase inhibitor, in chronic myelogenous leukaemia has
led to a rapid exploration of the potential of this new drug in
other fibrotic conditions in experimental models as well as in
severe IMIDs in humans.

Most importantly, however, targeted therapeutic interven-
tions 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. Even more striking, some
pathways appear to play a role in one type of organ involvement
but not in others within 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 pso-
riatic arthritis.

Taken together, these examples indicate that the concept of
IMIDs does not mean that all targeted anti-inflammatory ther-
apieties should per se be considered in all conditions, but illustrate
how a better understanding of disease-specific pathophysologi-
cal 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 modu-
late 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 dis-
order 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, classi-
cal 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 cli-
nical 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 ran-
domised 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 mor-
bitity 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 irra-
tional 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. 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. 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. The heterogeneous
presentation, the variable course of the disease (from spontane-
ous remission to irreversible organ loss) and the lack of interna-
tionally 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. As lung


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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. 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. 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. 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. 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. The clinical efficacy of TNF blockade has been confirmed in a randomised trial of the soluble TNF receptor etanercept in mucocutaneous BD. 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. 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, BD, 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>
<thead>
<tr>
<th>RCTs</th>
<th>Open trials</th>
<th>Case series</th>
<th>Outcome</th>
<th>Drug</th>
<th>References</th>
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<td>IFX</td>
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<tr>
<td>n=93</td>
<td>Positive</td>
<td>IFX</td>
<td>Judson et al&lt;sup&gt;29&lt;/sup&gt;</td>
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<td>n=13</td>
<td>Mixed</td>
<td>IFX</td>
<td>Rossman et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=9</td>
<td>Negative</td>
<td>ETN</td>
<td>Baughman et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
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. On the other hand, the aetiological diversity and the potential risk of deterioration of underlying infectious or demyelinating 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, even though two open prospective studies with etanercept did show beneficial effects. 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 severely 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 blocker in fever syndromes and Still’s disease, the use of B cell-directed biological agents in autoimmune-mediated conditions associated such as antineutrophil cytoplasmic antibody-associated vasculitis and even the use of nonbiological targeted therapies such as the previously mentioned tyrosine kinase inhibitors in fibrótic conditions. Accordingly, the

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

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Open trial</th>
<th>Case series</th>
<th>Outcome</th>
<th>Drug</th>
<th>References</th>
</tr>
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<td>Melikoglu et al</td>
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<tr>
<td>n=6</td>
<td>Positive</td>
<td>IFX</td>
<td>Naganuma M. Inflamm Bowel Dis 2008;14:1259–64.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
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 cornerstone 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.

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

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Open trials</th>
<th>Case series</th>
<th>Outcome</th>
<th>Drug</th>
<th>References</th>
</tr>
</thead>
<tbody>
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<td>Negative</td>
<td>ETN</td>
<td>Foster et al59</td>
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<td>n=7</td>
<td>Negative</td>
<td>ETN</td>
<td>Smith et al60</td>
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</tr>
<tr>
<td>n=10</td>
<td>Positive</td>
<td>ETN</td>
<td>Reiff et al62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
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 or discuss the management of specific conditions.

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-efficiency) 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 individual patients according to their genetic, biological or phenotypic profile. We still perform ‘experimental’ medicine in each individual patients according to their genetic, biological or phenotypic profile. We still perform ‘experimental’ medicine in each individual patients according to their genetic, biological or phenotypic profile. We still perform ‘experimental’ medicine in each individual patients according to their genetic, biological or phenotypic profile. We still perform ‘experimental’ medicine in each individual patients according to their genetic, biological or phenotypic profile. We still perform ‘experimental’ medicine in each individual patients according to their genetic, biological or phenotypic profile. We still perform ‘experimental’ medicine in each individual patients according to their genetic, biological or phenotypic profile.

Finally, the 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, standardisation of 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.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

47. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. *Ophthalmology* 2004;111:491–500; discussion 500.


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