Received: 3 March 2022 | Accepted: 23 April 2022

DOI: 10.1111/eci.13805

NARRATIVE REVIEW

WILEY

# Informed consent and biological agents in rheumatology and internal medicine

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## Abstract

**Background:** The need for highly effective therapies in rheumatologic diseases has led to the widespread and growing use of a heterogeneous class of molecules called biological agents. The increasing experience with biological agents has raised concerns about safety and efficacy issues that need to be discussed in the informed consent acquisition process.

**Methods:** The authors performed a review of the literature on biological agents focusing on their most important characteristics concerning the informed consent procedures.

**Results:** No studies specifically addressed the issue of informed consent in patients receiving biological agents. Several studies reported data about off-label use of biological agents usually with no obvious attention to informed consent shortcomings.

**Conclusion:** The reported association between biological agents and serious infections or malignancies, including reactivation of latent tuberculosis, needs specific disclosure in informed consent acquisition, together with information about the possible efficacy in clinical contexts often characterized by resistance to previous treatments. Ethical and clinical issues bound to the need for experimenting with new agents with potentially serious adverse effects deserve specific attention. Studies aimed at evaluating mental capacity to consent in subjects receiving biological agents are required.

KEYWORDS

biological agents, informed consent, mental capacity, rheumatology

## 1 | INTRODUCTION

Informed consent is a prerequisite to every diagnostic and therapeutic medical procedure, and to participate in clinical research. To provide valid informed consent several components are required including (a) voluntariness of the decision-making process, (b) accurate and complete information disclosure and (c) the patient's capacity to consent to treatment or clinical research.[1] Informed consent acquisition process might also be influenced by language barriers, cultural and religious beliefs.[2,3]

Evidence exists indicating that several clinical populations are at risk of mental incapacity to give informed consent to treatment, especially those patients characterized by cognitive impairment or those suffering from mental disorders.[4] Among known specific risk factors for incapacity are psychiatric symptoms, such as mania and psychosis, rather than specific psychiatric diagnoses.[5] Impaired treatment decision-making capacity also proved common and often unrecognized in acute medical inpatients.[6]

There is evidence supporting an association between rheumatologic diseases, cognitive impairment and psychiatric disorders, including a specific association between rheumatic diseases and mood disorders.[7] A significant number of patients with early-onset long-term systemic lupus erythematosus could moreover develop psychosis and cognitive dysfunction.[8] Significant psychiatric morbidity has also been reported in pemphigus and psoriasis,[9] and other immune-mediated inflammatory diseases potentially benefiting from treatment with biological agents,[10] including inflammatory bowel disease.[11]

Since neuropsychiatric morbidity is frequent in rheumatologic diseases, the risk of impairment in decisional capacity should be carefully considered in such patients, including possible subtle alterations of mental capacity to give informed consent. Furthermore, we argue that there is a need for specific careful procedures to acquire informed consent in rheumatologic settings, which is even stronger in those patients who are going to receive biological agents, due to the specific efficacy and tolerability profile, the peculiar pharmacological characteristics.

Most of the biological agents present an extremely complex safety profile thus requiring a significant cognitive effort to be adequately understood and appreciated by patients. Associations with other medications frequently used in moderate to severe rheumatologic diseases (e.g. corticosteroids, classic immunosuppressive drugs or cytotoxic agents) have also the possibility to induce unwanted psychotropic effects, including mood alterations and anxiety. Mood alterations can impair the decisional capacity,[12] which is a well-known issue for corticosteroid regimens.[10] Moreover, possible psychic effects of biological agents and of combination therapies are yet to be completely clarified.

**Key points**

- Biological agents represent a useful alternative for treating rheumatologic debilitating diseases.
- No studies specifically addressed the issue of informed consent for biological agents and ethical aspects of clinical research are neglected.
- Given the importance of biological agents, studies concerning patients' decision-making capacity and perception of the risk–benefit ratio of such therapies deserve specific attention.

Finally, the lack of definitive evidence about the long-term effects of biological agents, including physical and psychotropic ones, and the risk of developing malignancies and/or serious infections[13] deserves specific attention in information disclosure during the consent acquisition process.

The present review is firstly aimed at providing an overview of the principal clinical and medical-legal concepts pertaining to informed consent. The manuscript will then specifically focus on the most important characteristics of principal biological agents and their possible influence on informed consent procedures. Finally, we will briefly discuss the procedures useful for evaluating patients' capacity to give informed consent in rheumatologic clinical settings.

## 2 | INFORMED CONSENT TO MEDICAL TREATMENT

According to the principle of autonomy, many legal regulations of modern countries allow competent patients to accept or refuse medical treatment. It should be emphasized that assent does not equate to give informed consent. To ensure freedom of choice, physicians should always evaluate patients' degree of capacity to consent. Mental capacity to consent can be reliably assessed by several tools that have been developed for clinical and research settings.[14]

The most acknowledged mental capacity framework relies on a multidimensional model[15] encompassing several abilities, which must all be effective to ensure the patient's capacity. Correct and complete information is among the fundamental prerequisites of informed consent, accordingly the patient must have the ability to understand her/his disorder's main features, and the specific nature of the treatment proposed. Understanding of information must include potential risks and benefits, including those associated with no treatment and implications of possible

treatment alternatives. Such information disclosure could be complex if considering combination therapies, which are common in rheumatology (e.g. methotrexate plus a tumour necrosis factor inhibitor), due to side effects overlap and possibly unpredictable individual side effects.

If the disclosed information has been adequately understood and retained, a competent patient should be also able to appreciate her/his own medical condition and the likely consequences of treatment options. Appreciating information in informed consent procedures requires the acknowledgment (a) to suffer from the disease that has been diagnosed and its main symptoms and outcomes; (b) to potentially benefit from the expected therapeutic effects of the therapy.

Patients should be able to manipulate the disclosed information about diagnosis and treatment rationally and logically, to make assumptions on possible everyday effects of treatments and to compare different treatment alternatives (reasoning). Finally, patients should be able to express a choice by communicating their decision in a clear and nonambivalent way. Among reliable useful clinical tools to assess treatment decision-making capacity are the MacArthur Competence Assessment Tool for Treatment (MacCAT-T)[16] and the Aid to Capacity Evaluation (ACE).[17]

## 3 | INFORMED CONSENT TO CLINICAL RESEARCH

Patients involved in pharmacological clinical research protocols, including placebo-controlled randomized controlled trials, case studies and observational studies, must be capable to give valid informed consent to be enrolled in the study. Since participation in pharmacological trials might be potentially more threatening than receiving ordinary treatment, in which safety and efficacy profiles are well-established, the consent procedures must be even more accurate.

The juridical and ethical principles underlying informed consent to clinical research are analogous to those about consent to treatment. Nonetheless, it must be emphasized the difference existing between clinical and research settings, which is incidental to the level of clinical uncertainty often present in research protocols. A proper balance between protecting patients with reduced decision-making abilities and the need for scientific empirical evidence must be addressed.

Controversy resides in the medical decision to push the therapeutic boundaries to achieve possible clinical efficacy in patients who had had a poor response to traditional therapy by using medications not indicated for the specific disease. The off-label use of biological agents—a nonordinary yet frequent approach—is a good example of such an enthusiastic approach and will be analysed in the following paragraph, since it presents specific informed consent issues.

In the case of research studies, baseline and longitudinal monitoring of participants' level of capacity is advantageous. Even though the signature on an informed consent form could represent an indispensable legal requirement, it does not necessarily imply that the patient has a good understanding of the real nature of the research protocol.[18] Therapeutic misconception has proved frequent[18,19] and could represent a significant source of bias, especially in those patients suffering from chronic debilitating or painful conditions who have shown partial or poor response to previous ordinary treatment. The clinical research version of the MacArthur Competence Assessment Tool (MacCAT-CR)[20] has proved reliable for assessing mental capacity for research participation.

## 4 | CRITICAL INFORMED CONSENT-RELATED CHARACTERISTICS OF BIOLOGICAL AGENTS

Table 1 provides an overview of official therapeutic indications (by the European Medicine Agency approval) and main warnings of clinically available biologic agents in rheumatology (Table 1). Meanwhile, the agents' most common off-label uses are listed in Table 2.

## 5 | DISCUSSION

Most of the medical conditions requiring the use of biological agents are characterized by moderate to severe stages of chronic debilitating diseases. Although were not included in the present paper, biosimilar medicines deserve a specific mention as their production process does not ensure full interchangeability with original biological medicines.[66]

Most biologicals require that the patients have undergone previous trials with other conventional therapies usually characterized by significant toxicity, which represents another source of burden. Furthermore. the mechanism of action of biological agents, and possible interactions and side effects are complex and not easy to understand. Rheumatologic patients moreover often present clinically significant depressive and anxious symptoms. Taken together such considerations underline the intricacy of the informed consent acquisition process and recommend the need for a mental capacity status assessment of patients eligible to receive biologic agents. Possible psychiatric

**TABLE 1** Therapeutic indications and warnings of biological agents in rheumatology

| Agent | Action | Therapeutic indications | Warnings |
|---|---|---|---|
| Adalimumab | TNF-α inhibitor | Active rheumatoid arthritis in combination with methotrexate in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including methotrexate has been inadequate; juvenile idiopathic arthritis; ankylosing spondylitis. Psoriatic arthritis. Chronic plaque psoriasis. Active moderate to severe Crohn's disease. Active moderate to severe ulcerative colitis. Adulthood and childhood refractory chronic uveitis. | Increased risk to develop active tuberculosis or hepatitis B in already infected subjects. Increased risk to develop a serious infection. Heart failure. Possible interactions with abatacept, anakinra, certolizumab, etanercept, golimumab, infliximab, methotrexate, rituximab and steroids such as dexamethasone, methylprednisolone, prednisone or prednisolone. Increased risk of children, teenagers and young adults to develop cancer including lymphoma. Possible problems with subjects affected by HIV, multiple sclerosis, Guillain Barré syndrome, optic neuritis, seizures, any type of cancer and hematologic diseases. Pregnancy and breastfeeding. |
| Certolizumab | TNF-α inhibitor | Active rheumatoid arthritis in combination with methotrexate in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including methotrexate has been inadequate. Psoriatic arthritis, ankylosing spondylitis, axial-spondyloarthritis and Crohn's disease. | See adalimumab. However, as certolizumab is a pegylated Fab fragment lacking an Fc portion, it does not cross the placenta[21] and is not detectable in maternal milk[22] and therefore can be safely administrated in pregnant and breastfeeding women. |
| Etanercept | TNF-α inhibitor | Rheumatoid arthritis in combination or not with methotrexate. Psoriatic arthritis. Plaque psoriasis. Juvenile idiopathic arthritis (age >2 years). Paediatric plaque psoriasis (age >6 years). Ankylosing spondylitis. | See adalimumab. |
| Golimumab | TNF-α inhibitor | Rheumatoid arthritis in combination with methotrexate, when the response to DMARDs therapy including methotrexate has been inadequate; active and progressive rheumatoid arthritis in adults not previously treated with methotrexate, ankylosing spondylitis and psoriatic arthritis. | See adalimumab. Possible serious interactions with anticoagulants such as warfarin; possible interactions with cyclosporine and theophylline. |
| Infliximab | TNF-α inhibitor | Rheumatoid arthritis in combination with methotrexate when the response to DMARDs, including methotrexate, has been inadequate. Severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs. Ankylosing spondylitis. Psoriasis and psoriatic arthritis. Crohn's disease in adults and children 6 years of age or older has not improved when treated with conventional therapies. Ulcerative colitis in adults and children 6 years of age or older has not improved when treated with conventional therapies. | See Golimumab. |

**TABLE 1** (Continued)

| Agent | Action | Therapeutic indications | Warnings |
|---|---|---|---|
| Anakinra | IL-1 receptor antagonist | Rheumatoid arthritis in combination with methotrexate, in adults with an inadequate response to methotrexate alone. Colchicine-resistant recurrent idiopathic pericarditis. | Should not be used in patients with severe renal impairment or neutropenia. The concurrent administration with TNF antagonists is not recommended. Hypersensitivity to E. coli-derived proteins. Increased incidence of serious infections should not be initiated in patients with active infections. Unknown safety and efficacy in immunosuppressed patients or patients with chronic infections. Unknown carcinogenic potential in animals. No adequate and well-controlled studies on pregnant or nursing women. |
| Abatacept | Inhibitors of T lymphocyte activation | Rheumatoid arthritis in combination with methotrexate in adults with an inadequate response to previous therapy with one or more DMARDs including methotrexate. Polyarticular juvenile idiopathic arthritis in combination with methotrexate in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs. Psoriatic arthritis. | Unknown clinical risk of carcinogenesis. Patients should not receive live vaccines while taking abatacept and for 3 months after discontinuation. Risk of developing progressive multifocal leukoencephalopathy. No adequate safety data in pregnant or nursing women nor in patients with renal and hepatic impairment. Depression, anxiety and sleep disorder are reported as uncommon adverse reactions. Dizziness and reduced visual acuity have been reported as common and uncommon adverse reactions, respectively, in such cases driving and use of machinery should be avoided. |
| Tocilizumab | IL-6 inhibitor | Rheumatoid arthritis in combination with methotrexate in adults with an inadequate response to previous therapy with one or more DMARDs including methotrexate. Acute juvenile idiopathic arthritis (in children >2 years with inadequate response to previous treatment with FANS and systemic corticosteroids). Glucocorticoid-resistant giant cell arteritis. | See Golimumab. Possible interactions with nonsteroidal anti-inflammatory drugs and cholesterol-lowering medications. |
| Rituximab | CD20-positive B-cell inhibitor | Severe active rheumatoid arthritis in combination with methotrexate in adults with an inadequate response to previous therapy with one or more DMARDs including methotrexate or a first biologic drug. ANCA-associated systemic vasculitis. Non-Hodgkin's lymphoma. Chronic lymphocytic leukaemia. | Increased risk of infections, it should not be administered to patients with an active severe infection or severely immunocompromised patients. Rituximab is contraindicated in severe heart failure or uncontrolled cardiac disease. Increased risk of infections and progressive multifocal leukoencephalopathy. The concomitant use of rituximab and antirheumatic therapies other than methotrexate is not recommended. Unknown safety of immunization with live viral vaccines. No adequate and well-controlled studies on pregnant women, should not be used during breastfeeding; contraceptive methods during treatment and for 12 months following rituximab therapy should be used. |

**TABLE 2** Commonest off-label uses of biological agents in rheumatology

| Agent | Off-label use |
|---|---|
| Adalimumab | Pyoderma gangrenosum,[23] cutaneous sarcoidosis,[24] Behçet's disease,[25] childhood refractory chronic uveitis,[26] IgA pemphigus,[27] multicentric reticulohistiocytosis,[28] aphthous stomatitis,[29] pityriasis rubra pilaris.[30] |
| Certolizumab | Paediatric inflammatory bowel disease.[31] |
| Etanercept | Anorexia/weight loss syndrome in patients with advanced cancer,[32] diabetic macular edema,[33] colchicine-resistant familial Mediterranean fever,[34] subcorneal pustular dermatosis,[35] pityriasis rubra pilaris,[30] pemphigus,[36] paediatric Behçet's disease,[37] Behçet's disease.[38] |
| Golimumab | Uveitis,[39] refractory juvenile idiopathic arthritis-associated uveitis.[40] |
| Infliximab | Pityriasis rubra pilaris,[30] idiopathic hypereosinophilic syndrome,[41] cachexia in advanced pancreatic cancer patients,[42] refractory retinal vasculitis due to sarcoidosis,[43] cardiac sarcoidosis,[44] Takayasu arteritis,[45] refractory dermatomyositis,[46] steroid-resistant graft-versus-host disease,[47] complex regional pain syndrome,[48] hidradenitis suppurativa,[49] pyoderma gangrenosum,[50] Behçet's disease,[51] childhood refractory chronic uveitis,[26] refractory neuro-Behçet.[52] |
| Anakinra | Colchicine-resistant familial Mediterranean fever,[53] Schnitzler's syndrome,[54] Muckle-Wells syndrome,[55] acute gout,[56] hidradenitis suppurativa.[57] |
| Abatacept | Systemic lupus erythematosus.[58] |
| Tocilizumab | Refractory pemphigus foliaceus and Behçet's disease,[59] refractory cutaneous lupus,[60] refractory neuro-Behçet,[52] adult-onset Still's disease,[61] amyloidosis,[61] multiple myeloma,[61] polymyalgia rheumatic,[61] relapsing polychondritis,[61] remitting seronegative symmetrical synovitis with pitting edema-syndrome,[61] systemic lupus erythematosus,[61] systemic sclerosis,[61] Takayasu arteritis.[61] |
| Rituximab | Immune thrombocytopenia in children,[62] refractory systemic lupus erythematosus,[63] immune-mediated glomerular diseases,[64] progressive multiple sclerosis.[65] |

comorbidities represent another important source of criticality in informed consent acquisition procedures.

The peculiar safety profile of most biological agents includes the risk of reactivation of latent tuberculosis infection (LTBI). Such information should be disclosed to the patient who must also acknowledge uncertainty concerning the diagnostic accuracy of current LTBI screening methods. An analogous consideration could be argued for the risk of developing malignancies, which nowadays have been demonstrated to be intrinsically associated with rheumatoid arthritis. Due to this uncertainty, the relevance of the patient–doctor relationship during therapies with this class of compounds is of paramount importance.

In the case of research protocols, the analysis of the reasons for participation could find flawed informed consent. The risk of therapeutic misconception in research protocols or case studies involving biological medicines should be carefully addressed although to date apparently overlooked.

Other issues may be linked to a 'last resort' approach of a significant percentage of patients to biological agents. The patient's perception of her/his own condition might be biased, to give an example, by an urgent desire for relief from severe pain, which might entail underestimation of risks and overestimation of possible benefits.

Finally, another ethical issue stems from the use of biological agents in children with rheumatic diseases, especially concerning the risk of malignancies and infections including reactivation of LTBI,[67,68] which must be carefully evaluated during treatment. Further research aimed at evaluating mental capacity and psychiatric comorbidities in rheumatologic patients is advisable.

In such context, promoting specific communication strategies within the doctor–patient relationship represents a relevant objective for physicians. Although it is difficult to assess doctor–patient communication effectiveness, several authors proposed different communication strategies, including the use of visual and technological aids.[69,70]

The correct strategy of cutting-edge medicine, especially in the cases of delicate drug administration such as in rheumatology, must be understood not only as a relief from pain and concern for the safety of the treatment but also as the achievement of good clinical results over time. This is even more important in the administration of biological agents that have possible interactions and side effects on patients with clinically significant depressive and anxious dimensions.

## 6 | CONCLUSION

Biological agents represent useful means for treating rheumatologic debilitating diseases, however no studies specifically addressed the issue of informed consent for biological agents and ethical aspects of clinical research are neglected. Future studies concerning patients' decision-making capacity and perception of the risk-benefit ratio of such therapies are needed.

### AUTHOR CONTRIBUTIONS

GM involved in conceptualization and writing—original draft; FI involved in methodology; SF involved in writing—review and editing; IG involved in writing—review and editing; MB involved in investigation; BS involved in investigation; DF involved in investigation; RC involved in supervising.

### CONFLICT OF INTEREST

The authors have no relevant financial or nonfinancial interests to disclose.

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### REFERENCES

1. Lidz CW, Meisel A, Zerubavel E. In: Lidz CW, ed. *Informed Consent: A study of decisionmaking in psychiatry*. Guilford Publications; 1984:167-187.
2. Shapiro D, Morley G. Evaluating decision-making capacity: when a false belief about ventilators is the reason for refusal of life-sustaining treatment. *J Clin Ethics*. 2022;33(1):50-57.
3. Ovrom E, Zemene Y, Gerndt S, Andrade V, Wiedermann J. Cultural competency and surgical decision making in otolaryngology. *Otolaryngol Head Neck Surg*. 2022;166:793-794. doi:10.1177/01945998221083848
4. Mandarelli G, Parmigiani G, Tarsitani L, Frati P, Biondi M, Ferracuti S. The relationship between executive functions and capacity to consent to treatment in acute psychiatric hospitalization. *J Empir Res Hum Res Ethics*. 2012;7(5):63-70. doi:10.1525/jer.2012.7.5.63
5. Cairns R, Maddock C, Buchanan A, et al. Prevalence and predictors of mental incapacity in psychiatric in-patients. *Br J Psychiatry*. 2005;187:379-385. doi:10.1192/bjp.187.4.379
6. Raymont V, Bingley W, Buchanan A, et al. Prevalence of mental incapacity in medical inpatients and associated risk factors: cross-sectional study. *Lancet*. 2004;364(9443):1421-1427. doi:10.1016/S0140-6736(04)17224-3
7. Frol AB, Vasquez A, Getahun Y, Pacheco M, Khan DA, Brown ES. A comparison of clinician-rated neuropsychological and self-rated cognitive assessments in patients with asthma and rheumatologic disorders. *Allergy Asthma Proc*. 2013;34(2):170-175. doi:10.2500/aap.2013.34.3642
8. Lim LSH, Lefebvre A, Benseler S, Silverman ED. Longterm outcomes and damage accrual in patients with childhood systemic lupus erythematosus with psychosis and severe cognitive dysfunction. *J Rheumatol*. 2013;40(4):513-519. doi:10.3899/jrheum.121096
9. Kumar V, Mattoo SK, Handa S. Psychiatric morbidity in pemphigus and psoriasis: a comparative study from India. *Asian J Psychiatr*. 2013;6(2):151-156. doi:10.1016/j.ajp.2012.10.005
10. Walker JR, Graff LA, Dutz JP, Bernstein CN. Psychiatric disorders in patients with immune-mediated inflammatory diseases: prevalence, association with disease activity, and overall patient well-being. *J Rheumatol Suppl*. 2011;88:31-35. doi:10.3899/jrheum.110900
11. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflamm Bowel Dis*. 2009;15(7):1105-1118. doi:10.1002/ibd.20873
12. Misra S, Socherman R, Hauser P, Ganzini L. Appreciation of research information in patients with bipolar disorder. *Bipolar Disord*. 2008;10(5):635-646. doi:10.1111/j.1399-5618.2008.00609.x
13. Chung SA, Seo P. Advances in the use of biologic agents for the treatment of systemic vasculitis. *Curr Opin Rheumatol*. 2009;21(1):3-9. doi:10.1097/BOR.0b013e32831d28b3
14. Lamont S, Jeon Y-H, Chiarella M. Assessing patient capacity to consent to treatment: an integrative review of instruments and tools. *J Clin Nurs*. 2013;22(17–18):2387-2403. doi:10.1111/jocn.12215
15. Appelbaum PS. Clinical practice. Assessment of patients' competence to consent to treatment. *N Engl J Med*. 2007;357(18):1834-1840. doi:10.1056/NEJMcp074045
16. Grisso T, Appelbaum PS, Hill-Fotouhi C. The MacCAT-T: a clinical tool to assess patients' capacities to make treatment decisions. *Psychiatr Serv*. 1997;48(11):1415-1419. doi:10.1176/ps.48.11.1415
17. Etchells E, Darzins P, Silberfeld M, et al. Assessment of patient capacity to consent to treatment. *J Gen Intern Med*. 1999;14(1):27-34. doi:10.1046/j.1525-1497.1999.00277.x
18. Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. *IRB*. 2004;26(2):1-8.
19. Appelbaum PS, Anatchkova M, Albert K, Dunn LB, Lidz CW. Therapeutic misconception in research subjects: development

and validation of a measure. *Clin Trials*. 2012;9(6):748-761. doi:10.1177/1740774512456455
20. Appelbaum PS, Grisso T. *MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research*. Professional Resource Press; 2001.
21. Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann Rheum Dis*. 2018;77(2):228-233. doi:10.1136/annrheumdis-2017-212196
22. Clowse ME, Förger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. *Ann Rheum Dis*. 2017;76(11):1890-1896. doi:10.1136/annrheumdis-2017-211384
23. Rousset L, de Masson A, Begon E, et al. Tumor necrosis factor-α inhibitors for the treatment of pyoderma gangrenosum not associated with inflammatory bowel diseases: a multicenter retrospective study. *J Am Acad Dermatol*. 2019;80(4):1141-1143. doi:10.1016/j.jaad.2018.10.006
24. Lower EE, Sturdivant M, Grate L, Baughman RP. Use of third-line therapies in advanced sarcoidosis. *Clin Exp Rheumatol*. 2020;38(5):834-840.
25. Aksoy A, Yazici A, Omma A, et al. Efficacy of TNFα inhibitors for refractory vascular Behçet's disease: a multicenter observational study of 27 patients and a review of the literature. *Int J Rheum Dis*. 2020;23(2):256-261. doi:10.1111/1756-185X.13778
26. Simonini G, Taddio A, Cattalini M, et al. Superior efficacy of adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: adalimumab as starting anti-TNF-α therapy in childhood chronic uveitis. *Pediatr Rheumatol Online J*. 2013;11:16. doi:10.1186/1546-0096-11-16
27. Howell SM, Bessinger GT, Altman CE, Belnap CM. Rapid response of IgA pemphigus of the subcorneal pustular dermatosis subtype to treatment with adalimumab and mycophenolate mofetil. *J Am Acad Dermatol*. 2005;53(3):541-543. doi:10.1016/j.jaad.2005.02.051
28. Shannon SE, Schumacher HR, Self S, Brown AN. Multicentric reticulohistiocytosis responding to tumor necrosis factor-alpha inhibition in a renal transplant patient. *J Rheumatol*. 2005;32(3):565-567.
29. Vujevich J, Zirwas M. Treatment of severe, recalcitrant, major aphthous stomatitis with adalimumab. *Cutis*. 2005;76(2):129-132.
30. Petrof G, Almaani N, Archer CB, Griffiths WAD, Smith CH. A systematic review of the literature on the treatment of pityriasis rubra pilaris type 1 with TNF-antagonists. *J Eur Acad Dermatol Venereol*. 2013;27(1):e131-e135. doi:10.1111/j.1468-3083.2012.04456.x
31. de Bie CI, Escher JC, de Ridder L. Antitumor necrosis factor treatment for pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18(5):985-1002. doi:10.1002/ibd.21871
32. Jatoi A, Dakhil SR, Nguyen PL, et al. A placebo-controlled double blind trial of etanercept for the cancer anorexia/weight loss syndrome: results from N00C1 from the north central cancer treatment group. *Cancer*. 2007;110(6):1396-1403. doi:10.1002/cncr.22944
33. Pascual-Camps I, Hernández-Martínez P, Monje-Fernández L, et al. Update on intravitreal anti-tumor necrosis factor alpha therapies for ocular disorders. *J Ophthalmic Inflamm Infect*. 2014;4:26. doi:10.1186/s12348-014-0026-8
34. Seyahi E, Ozdogan H, Celik S, Ugurlu S, Yazici H. Treatment options in colchicine resistant familial Mediterranean fever patients: thalidomide and etanercept as adjunctive agents. *Clin Exp Rheumatol*. 2006;24(5 Suppl 42):S99-S103.
35. Bedi MK. Successful treatment of long-standing, recalcitrant subcorneal pustular dermatosis with etanercept. *Skinmed*. 2007;6(5):245-247. doi:10.1111/j.1540-9740.2007.888109.x
36. Zhao CY, Murrell DF. Pemphigus vulgaris: an evidence-based treatment update. *Drugs*. 2015;75(3):271-284. doi:10.1007/s40265-015-0353-6
37. Watanabe S, Aizawa-Yashiro T, Tsuruga K, Kinjo M, Ito E, Tanaka H. A young girl with refractory intestinal Behçet's disease: a case report and review of literatures on pediatric cases who received an anti-tumor necrosis factor agent. *Rheumatol Int*. 2013;33(12):3105-3108. doi:10.1007/s00296-012-2628-5
38. Arida A, Fragiadaki K, Giavri E, Sfikakis PP. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. *Semin Arthritis Rheum*. 2011;41(1):61-70. doi:10.1016/j.semarthrit.2010.09.002
39. Tosi GM, Sota J, Vitale A, et al. Efficacy and safety of certolizumab pegol and golimumab in the treatment of non-infectious uveitis. *Clin Exp Rheumatol*. 2019;37(4):680-683.
40. William M, Faez S, Papaliodis GN, Lobo A-M. Golimumab for the treatment of refractory juvenile idiopathic arthritis-associated uveitis. *J Ophthalmic Inflamm Infect*. 2012;2(4):231-233. doi:10.1007/s12348-012-0081-y
41. Taverna JA, Lerner A, Goldberg L, Werth S, Demierre M-F. Infliximab as a therapy for idiopathic hypereosinophilic syndrome. *Arch Dermatol*. 2007;143(9):1110-1112. doi:10.1001/archderm.143.9.1110
42. Wiedenmann B, Malfertheiner P, Friess H, et al. A multicenter, phase II study of infliximab plus gemcitabine in pancreatic cancer cachexia. *J Support Oncol*. 2008;6(1):18-25.
43. Cruz BA, Reis DD, Araujo CAA. Refractory retinal vasculitis due to sarcoidosis successfully treated with infliximab. *Rheumatol Int*. 2007;27(12):1181-1183. doi:10.1007/s00296-007-0359-9
44. Uthman I, Touma Z, Khoury M. Cardiac sarcoidosis responding to monotherapy with infliximab. *Clin Rheumatol*. 2007;26(11):2001-2003. doi:10.1007/s10067-007-0614-1
45. Karageorgaki ZT, Mavragani CP, Papathanasiou MA, Skopouli FN. Infliximab in Takayasu arteritis: a safe alternative? *Clin Rheumatol*. 2007;26(6):984-987. doi:10.1007/s10067-006-0227-0
46. Dold S, Justiniano ME, Marquez J, Espinoza LR. Treatment of early and refractory dermatomyositis with infliximab: a report of two cases. *Clin Rheumatol*. 2007;26(7):1186-1188. doi:10.1007/s10067-006-0325-z
47. Yang J, Cheuk DKL, Ha SY, et al. Infliximab for steroid refractory or dependent gastrointestinal acute graft-versus-host disease in children after allogeneic hematopoietic stem cell transplantation. *Pediatr Transplant*. 2012;16(7):771-778. doi:10.1111/j.1399-3046.2012.01756.x
48. Dirckx M, Groeneweg G, Wesseldijk F, Stronks DL, Huygen FJPM. Report of a preliminary discontinued double-blind, randomized, placebo-controlled trial of the anti-TNF-α chimeric monoclonal antibody infliximab in complex regional pain syndrome. *Pain Pract*. 2013;13(8):633-640. doi:10.1111/papr.12078
49. Kawak S. Hidradenitis suppurativa. *Dis Colon Rectum*. 2019;62(11):1278-1280. doi:10.1097/DCR.0000000000001497

50. Hubbard VG, Friedmann AC, Goldsmith P. Systemic pyoderma gangrenosum responding to infliximab and adalimumab. *Br J Dermatol*. 2005;152(5):1059-1061. doi:10.1111/j.1365-2133.2005.06467.x
51. Sugimura N, Mizoshita T, Sugiyama T, et al. Real-world efficacy of adalimumab and infliximab for refractory intestinal Behçet's disease. *Dig Liver Dis*. 2019;51(7):967-971. doi:10.1016/j.dld.2018.10.024
52. Addimanda O, Pipitone N, Pazzola G, Salvarani C. Tocilizumab for severe refractory neuro-Behçet: three cases IL-6 blockade in neuro-Behçet. *Semin Arthritis Rheum*. 2015;44(4):472-475. doi:10.1016/j.semarthrit.2014.08.004
53. Şahin A, Derin ME, Albayrak F, Karakaş B, Karagöz Y. Assessment of effectiveness of anakinra and canakinumab in patients with colchicine-resistant/unresponsive familial Mediterranean fever. *Adv Rheumatol*. 2020;60(1):12. doi:10.1186/s42358-020-0117-1
54. Gellrich FF, Günther C. Schnitzler syndrome. *Hautarzt*. 2018;69(9):761-772. doi:10.1007/s00105-018-4250-2
55. Yamazaki T, Masumoto J, Agematsu K, et al. Anakinra improves sensory deafness in a Japanese patient with muckle-Wells syndrome, possibly by inhibiting the cryopyrin inflammasome. *Arthritis Rheum*. 2008;58(3):864-868. doi:10.1002/art.23261
56. Aouba A, Deshayes S, Frenzel L, et al. Efficacy of anakinra for various types of crystal-induced arthritis in complex hospitalized patients: a case series and review of the literature. *Mediat Inflamm*. 2015;2015:792173. doi:10.1155/2015/792173
57. van der Zee HH, Prens EP. Failure of anti-interleukin-1 therapy in severe hidradenitis suppurativa: a case report. *Dermatology*. 2013;226(2):97-100. doi:10.1159/000343221
58. Shamliyan TA, Dospinescu P. Additional improvements in clinical response from adjuvant biologic response modifiers in adults with moderate to severe systemic lupus erythematosus despite immunosuppressive agents: a systematic review and meta-analysis. *Clin Ther*. 2017;39(7):1479-1506.e45. doi:10.1016/j.clinthera.2017.05.359
59. Caso F, Iaccarino L, Bettio S, et al. Refractory pemphigus foliaceus and Behçet's disease successfully treated with tocilizumab. *Immunol Res*. 2013;56(2–3):390-397. doi:10.1007/s12026-013-8411-1
60. Makol A, Gibson LE, Michet CJ. Successful use of interleukin 6 antagonist tocilizumab in a patient with refractory cutaneous lupus and urticarial vasculitis. *J Clin Rheumatol*. 2012;18(2):92-95. doi:10.1097/RHU.0b013e31823ecd73
61. Alten R, Maleitzke T. Tocilizumab: a novel humanized anti-interleukin 6 (IL-6) receptor antibody for the treatment of patients with non-RA systemic, inflammatory rheumatic diseases. *Ann Med*. 2013;45(4):357-363. doi:10.3109/07853890.2013.771986
62. Liang Y, Zhang L, Gao J, Hu D, Ai Y. Rituximab for children with immune thrombocytopenia: a systematic review. *PLoS One*. 2012;7(5):e36698. doi:10.1371/journal.pone.0036698
63. Al-Adhoubi NK, Bystrom J. Systemic lupus erythematosus and diffuse alveolar hemorrhage, etiology and novel treatment strategies. *Lupus*. 2020;29(4):355-363. doi:10.1177/0961203320903798
64. Boumediene A, Vachin P, Sendeyo K, et al. NEPHRUTIX: a randomized, double-blind, placebo vs rituximab-controlled trial assessing T-cell subset changes in minimal change nephrotic syndrome. *J Autoimmun*. 2018;88:91-102. doi:10.1016/j.jaut.2017.10.006
65. Axelsson M, Malmeström C, Gunnarsson M, et al. Immunosuppressive therapy reduces axonal damage in progressive multiple sclerosis. *Mult Scler*. 2014;20(1):43-50. doi:10.1177/1352458513490544
66. Iskit AB. Key concepts in biosimilar medicines: what physicians must know. *North Clin Istanbul*. 2022;9(1):86-91. doi:10.14744/nci.2021.84669
67. Kilic O, Kasapcopur O, Camcioglu Y, Cokugras H, Arisoy N, Akcakaya N. Is it safe to use anti-TNF-α agents for tuberculosis in children suffering with chronic rheumatic disease? *Rheumatol Int*. 2012;32(9):2675-2679. doi:10.1007/s00296-011-2030-8
68. Zhao W-J, Deng J-H, Li C-F. Research progress in drug therapy of juvenile idiopathic arthritis. *World J Pediatr*. 2022;1-15. doi:10.1007/s12519-022-00530-8
69. Cox C, Fritz Z. What is in the toolkit (and what are the tools)? How to approach the study of doctor-patient communication. *Postgrad Med J*. 2022. doi:10.1136/postgradmedj-2021-140663
70. Zolnierek KBH, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care*. 2009;47(8):826-834. doi:10.1097/MLR.0b013e31819a5acc

**How to cite this article:** Mandarelli G, Iannone F, Ferracuti S, et al. Informed consent and biological agents in rheumatology and internal medicine. *Eur J Clin Invest*. 2022;00:e13805. doi: 10.1111/eci.13805