Updates in Rheumatology

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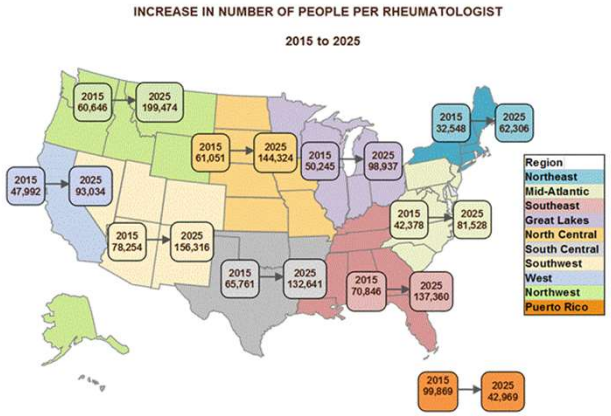
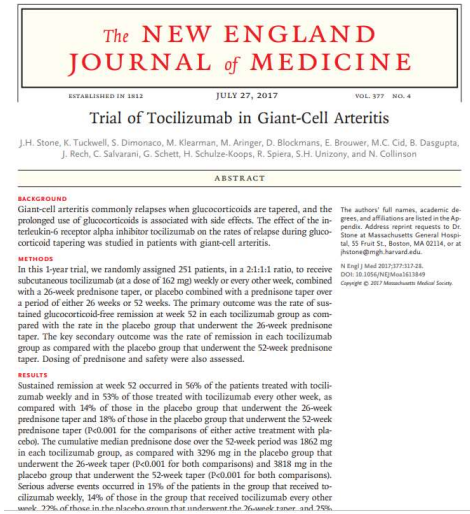
Disclosures

- None

Objectives

1. Understand the current and projected shortage of Rheumatologists in the Pacific Northwest
2. Updates on newer Rheumatology medications
    1. Psoriatic Arthritis
    2. Rheumatoid Arthritis
3. Discuss malignancy and cardiovascular risks in rheumatoid arthritis patients
4. Discuss 2022 classification criteria for giant cell arteritis
5. Updated Systemic Lupus Erythematosus classification criteria
6. Highlight updates in systemic sclerosis




The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 27, 2017 VOL. 377 NO. 4

Trial of Tocilizumab in Giant-Cell Arteritis

J.H. Stone, K. Tuckwell, S. Dimonaco, M. Klearman, M. Aringer, D. Blockmans, E. Brouwer, M.C. Cid, B. Dasgupta, J. Rech, C. Salvarani, G. Schett, H. Schulze-Koops, R. Spiera, S.H. Unizony, and N. Collinson

ABSTRACT

BACKGROUND

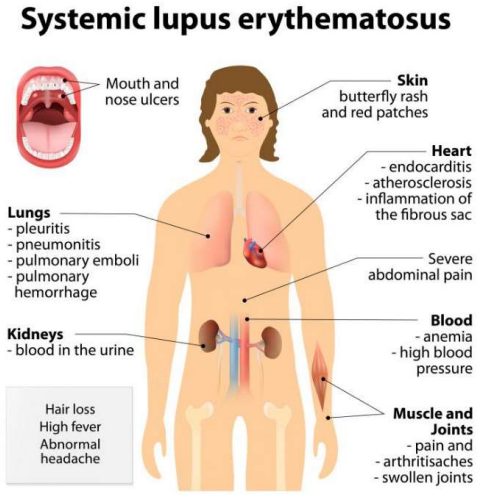
Giant-cell arteritis commonly relapses when glucocorticoids are tapered, and the prolonged use of glucocorticoids is associated with side effects. The effect of the interleukin-6 receptor alpha inhibitor tocilizumab on the rates of relapse during glucocorticoid tapering was studied in patients with giant-cell arteritis.

METHODS

In this 1-year trial, we randomly assigned 251 patients, in a 2:1:1:1 ratio, to receive subcutaneous tocilizumab (at a dose of 162 mg) weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. The primary outcome was the rate of sustained glucocorticoid-free remission at week 52 in each tocilizumab group as compared with the rate in the placebo group that underwent the 26-week prednisone taper. The key secondary outcome was the rate of remission in each tocilizumab group as compared with the placebo group that underwent the 52-week prednisone taper. Dosing of prednisone and safety were also assessed.

RESULTS

Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly and in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group that underwent the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper ($P<0.001$ for the comparisons of either active treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each tocilizumab group, as compared with 3296 mg in the placebo group that underwent the 26-week taper ($P<0.001$ for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper ($P<0.001$ for both comparisons). Serious adverse events occurred in 15% of the patients in the group that received tocilizumab weekly, 14% of those in the group that received tocilizumab every other



How hard is it to see a rheumatologist in the Pacific Northwest?

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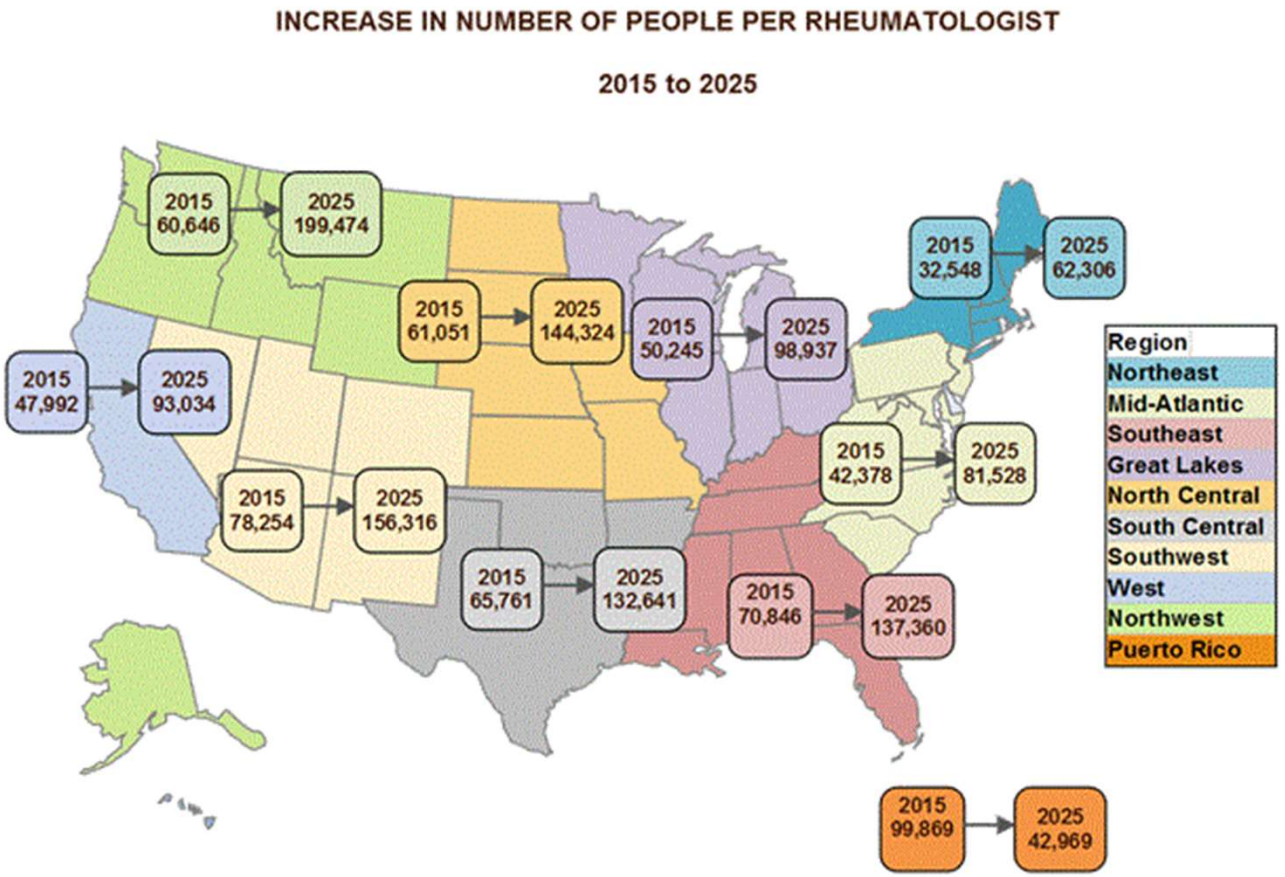
Figure 1. Adult Rheumatologists per Population, 2015 compared to 2025

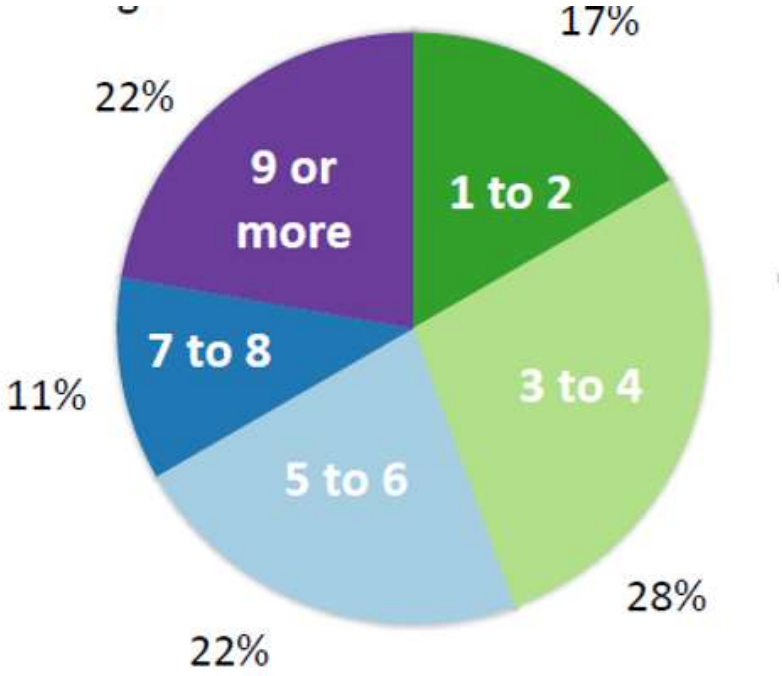


Lawrence-Wolff K, Hildebrand B, Monrad S, Ditmyer M, Fitzgerald J, Erickson A, Bass AR, Battafarano D. 2015 ACR/ARHP Workforce Study in the United States: A Maldistribution of Adult Rheumatologists [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10). http://acrabstracts.org/abstract/2015-acrarhp-workforce-study-in-the-united-states-a-maldistribution-of-adult-rheumatologists/. Accessed January 17, 2017.

Wait Time (in weeks) for a rheumatology clinic visit in Washington State

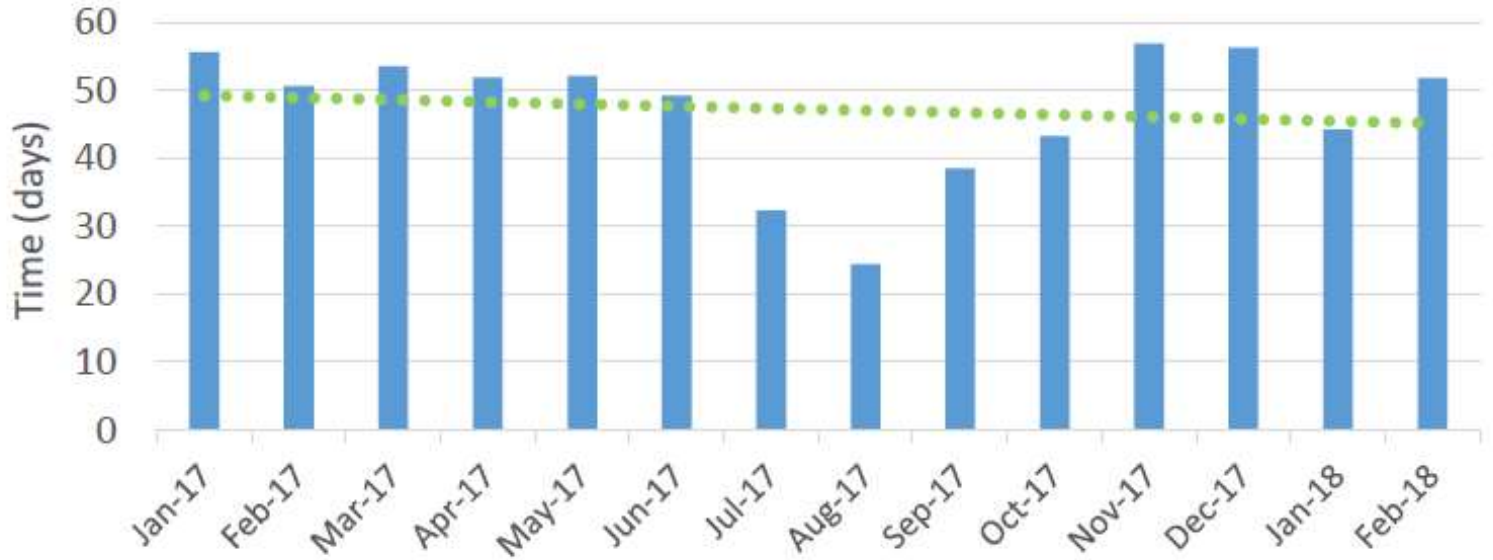
Rheumatologists are rare in Washington state. **In 2018, there were 125 adult rheumatologists in Washington state.** 1/3 are over age 60 and many are not full-time clinicians.

Many parts of the WWAMI region (Wyoming, Washington, Alaska, Montana, and Idaho) do not have a rheumatologist. The wait times to see a rheumatologist can be a year or longer.

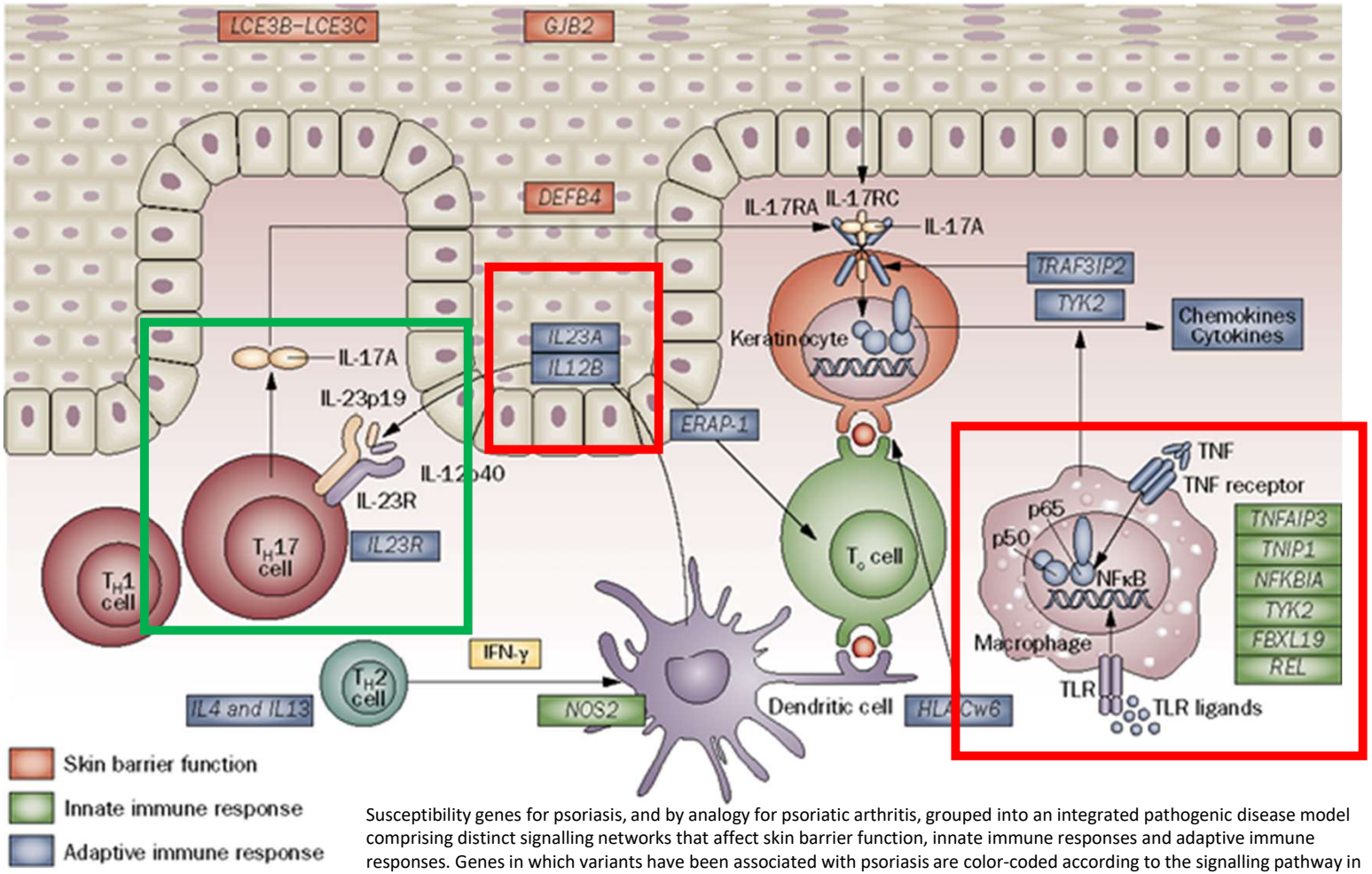


For our telephone survey, we identified a total of 89 rheumatology providers working at 42 practices in Washington State using the Washington Rheumatology Alliance, American College of Rheumatology (ACR) list-serve, and an internet search.

Figure 1: Average month-by-month time to rheumatology visit at Virginia Mason for new patients.



Psoriatic Arthritis Medication Updates

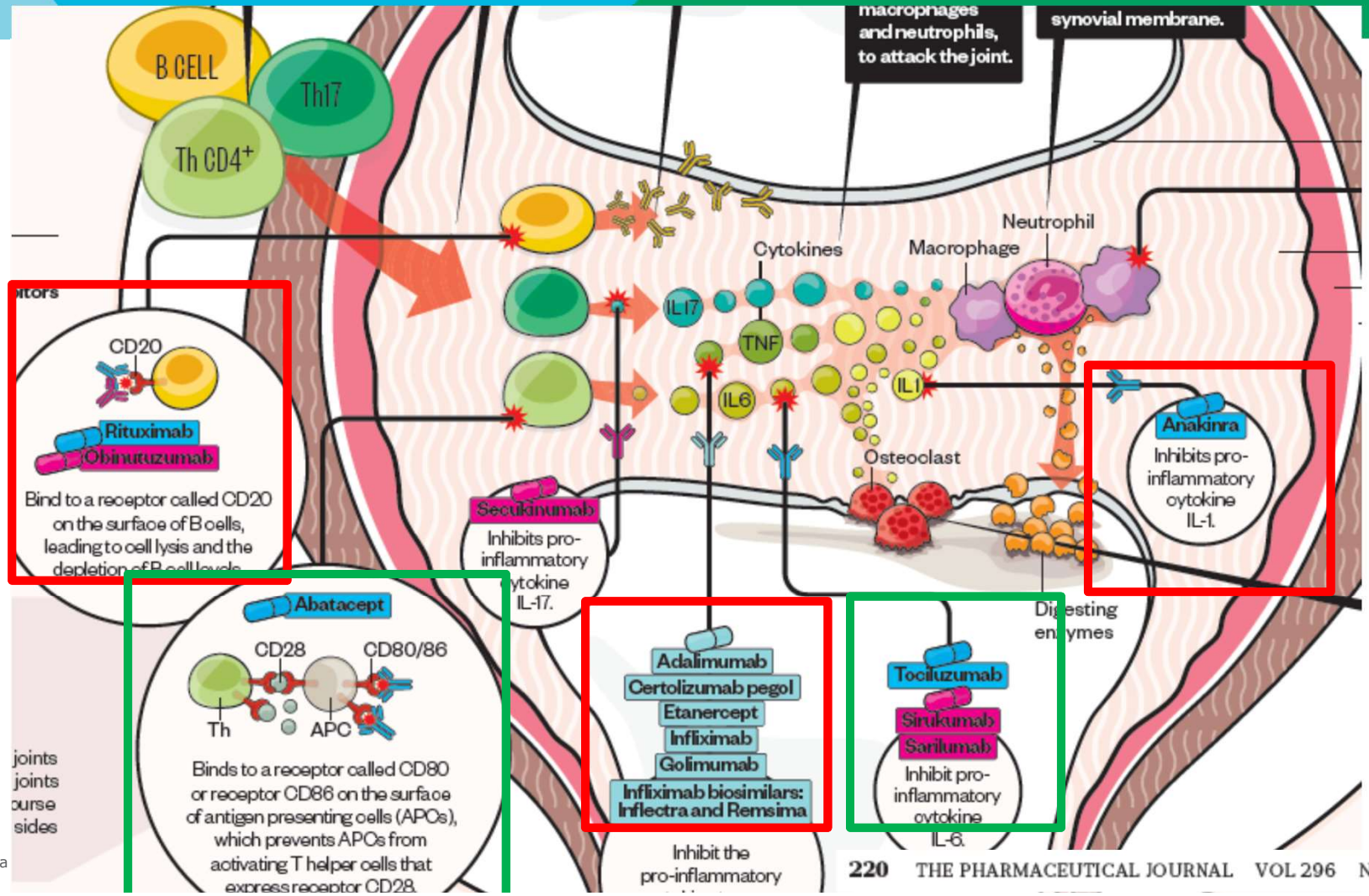


Susceptibility genes for psoriasis, and by analogy for psoriatic arthritis, grouped into an integrated pathogenic disease model comprising distinct signalling networks that affect skin barrier function, innate immune responses and adaptive immune responses. Genes in which variants have been associated with psoriasis are color-coded according to the signalling pathway in which they function. IFN: interferon; IL-17: interleukin-17; NFκB: nuclear factor κB; Tc cell: cytotoxic T cell; TH1 cell: T helper 1 cell; TH2 cell: T helper 2 cell; TH17 cell: T helper 17 cell; TLR: Toll-like receptor; TNF: tumour necrosis factor **Nature Reviews Rheumatology 7: 718–732, copyright 2011.**

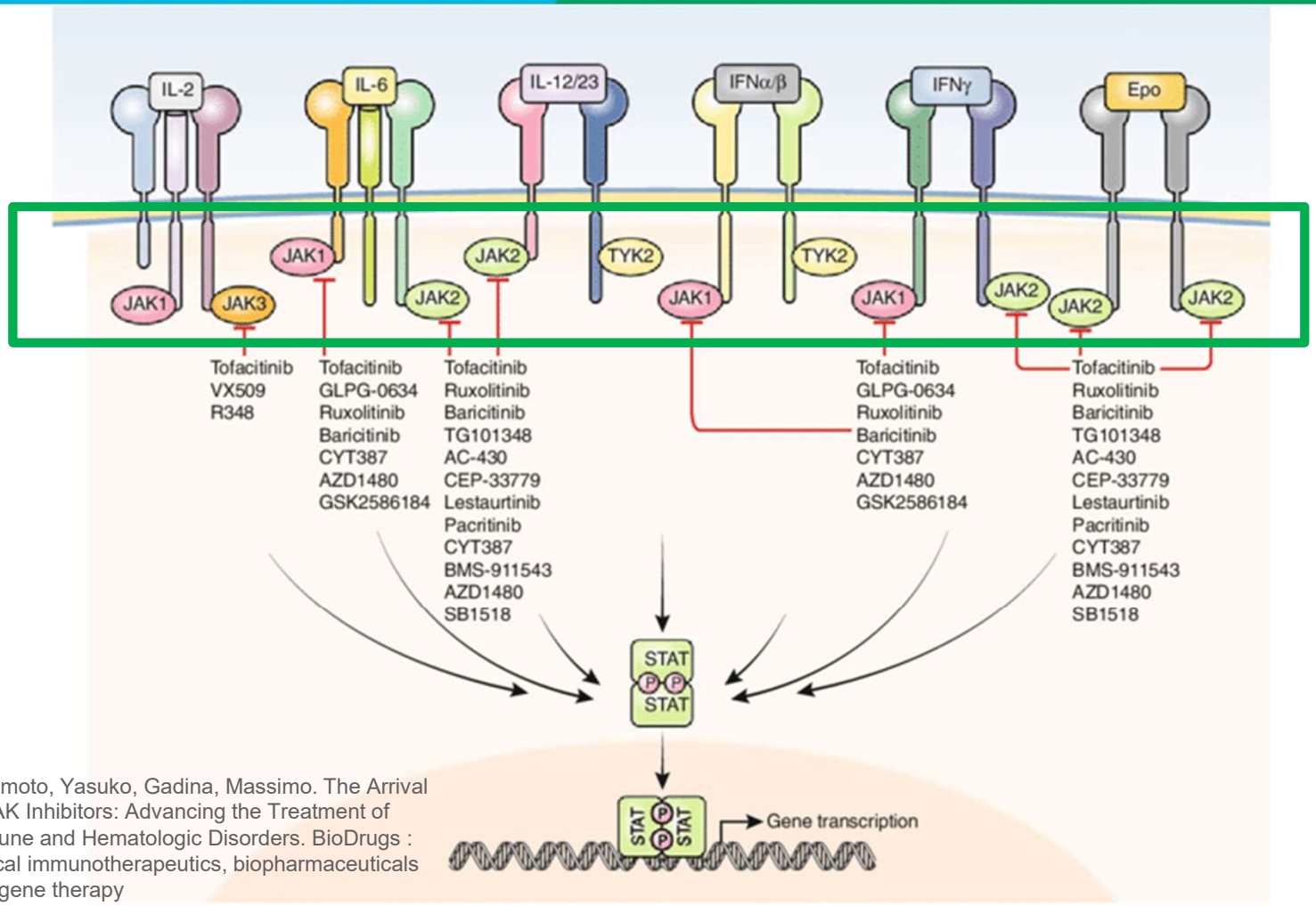
Psoriatic Arthritis Medication Updates

Medication / FDA Approval Date	Mechanism of Action	Common Side Effects	Monitoring Considerations
Apremilast (Otezla) **2014**	PDE4 inhibitor PO BID	Weight loss (20%) Diarrhea	Weight Loss Depression/Suicidality CBC and CMR q 3 mo
Secukinumab (Cosentyx) **2016**	IL 17A monoclonal ab SQ q month	URIs	IBD flare
Ixekizumab (Taltz) **2017**	IL 17A monoclonal ab SQ q month	URIs	IBD flare
Tofacitinib (Xeljanz) **2017**	JAK inhibitor 5 mg BID or 11 mg ER daily	Shingles, URIs, PE/DVT, GI perforation, skin cancer, heart attack, stroke	CBC q 3 mo LFTs q 3 mo Lipids q 6 mo Annual Derm
Golimumab (Simponi) **2017**	TNF inhibitor	Infections	CNS demyelination, heart failure, TB
Abatacept (Orencia) **2017**	CTLA-4 fusion protein inhibitor (Inhibits T cell activation)	Lower risk of URI and TB	Less effective for moderate-to-severe skin psoriasis; ?COPD flare
Guselkumab (Tremfya) **2020**	IL-23 inhibitor	URIs, gastroenteritis	Liver function tests, TB

Rheumatoid Arthritis Updates



Rheumatoid Arthritis Updates



Furumoto, Yasuko, Gadina, Massimo. The Arrival of JAK Inhibitors: Advancing the Treatment of Immune and Hematologic Disorders. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy

Rheumatoid Arthritis Updates

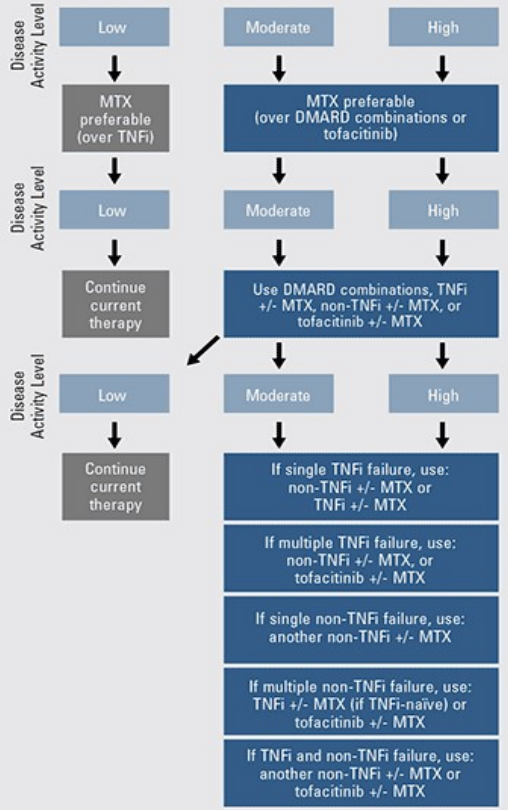
Medication / FDA approval date	Mechanism of action	Common SE	Monitoring Considerations
Abatacept (Orencia) **2011** *** 2017**	Blocks T cell activation SQ / IV		?COPD
***Tofacitinib (Xeljanz)** **2012** *** 2017**	JAK inhibitor PO BID/daily	URIs Zoster GI perforation Skin cancer PE/DVT Heart attack/stroke	CBC q 3 mo LFTs q 3 mo Lipids q 6 mo Annual Derm
Baricitinib (Olumiant) **2018**	JAK inhibitor PO daily	URIs Zoster GI perforation Skin cancer	CBC q 3 mo LFTs q 3 mo Lipids q 6 mo Annual Derm
Tocilizumab (Actemra) **2013**	IL-6 inhibition SQ q 2 wks / IV monthly	GI perforation	CBC q 3 mo LFTs q 3 mo Lipids q 6 mo
Sarilumab (Kevzara) **2017**	IL-6 inhibition SQ q 2 wks	GI perforation	CBC q 3 mo LFTs q 3 mo Lipids q 6 mo
Upadacitinib (Rinvoq) **2019**	JAK inhibitor PO daily	URI, fever, cough, nausea	CBC q 3 mo LFTs q 3 mo Lipids q 6 mo
* Approved for Psoriatic Arthritis			

Clinically Relevant Drugs Used in the Treatment of RA

Conventional Synthetic DMARDs
Hydroxychloroquine
Leflunomide
Methotrexate
Sulfasalazine
Targeted Synthetic DMARDs
Baricitinib
Tofacitinib
Biological DMARDs
TNF alpha inhibitors
Adalimumab
Certolizumab pegol
Etanercept
Golimumab
Infliximab
Anti–B-cell (CD20)
Rituximab
Anti–T-cell costimulation (CD80, CD86)
Abatacept
Anti–IL-6
Sarilumab
Tocilizumab

DMARD: disease-modifying antirheumatic drug; IL: interleukin; RA: rheumatoid arthritis; TNF: tumor necrosis factor.
Source: References 7, 8.

Abbreviated Treatment Algorithm for Established RA[a] (≥6 months of symptoms and DMARD naïve)



[a]According to American College of Rheumatology 2015 guidelines. DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitor.
Source: Reference 4.

Reference: March 15, 2019: https://www.uspharmacist.com/article/review-of-rheumatoid-arthritis-for-the-pharmacist

FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR)

FDA Drug Safety Communication

This is an update to the FDA Drug Safety Communication: Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate (/drugs/drug-safety-and-availability/safety-trial-finds-risk-blood-clots-lungs-and-death-higher-dose-tofacitinib-xeljanz-xeljanz-xr) issued on February 25, 2019.

Safety Announcement

[7-26-2019] The U.S. Food and Drug Administration has approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of tofacitinib (Xeljanz, Xeljanz XR), which is used in patients with ulcerative colitis. In addition, the approved use of tofacitinib for ulcerative colitis will be limited to certain patients who are not treated effectively or who experience severe side effects with certain other medicines. We approved these changes, including adding our most prominent *Boxed Warning*, after reviewing interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis (RA) that examined a lower and this higher dose of the medicine.

The 10 mg twice daily dose of tofacitinib is not approved for RA or psoriatic arthritis (PsA). This dose is only approved for ulcerative colitis for initial

Wollenhaupt et al. Arthritis Research & Therapy (2019) 21:89
https://doi.org/10.1186/s13075-019-1866-2

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study

Jürgen Wollenhaupt[1], Eun-Bong Lee[2], Jeffrey R. Curtis[3], Joel Silverfield[4], Ketti Terry[5], Koshika Soma[6], Chris Mojcik[6], Ryan DeMasi[7], Sander Strengholt[8], Kenneth Kwok[6], Irina Lazariciu[9], Lisy Wang[5*] and Stanley Cohen[10]

Abstract

Background: Final data are presented for the ORAL Sequel long-term extension (LTE) study evaluating the safety and efficacy of tofacitinib 5 mg and 10 mg twice daily (BID) for up to 9.5 years in patients with rheumatoid arthritis (RA).

Methods: Eligible patients had previously completed a phase 1, 2, or 3 qualifying index study of tofacitinib and received open-label tofacitinib 5 mg or 10 mg BID. Stable background therapy, including csDMARDs, was continued; adjustments to tofacitinib or background therapy were permitted at investigators' discretion. Assignment to dose groups (5 mg or 10 mg BID) was based on patients' average total daily dose. The primary objective was to determine the long-term safety and tolerability of tofacitinib 5 mg and 10 mg BID; the key secondary objective was to evaluate the long-term persistence of efficacy.

Results: Between February 5, 2007, and November 30, 2016, 4481 patients were enrolled. Total tofacitinib exposure was 16,291 patient-years. Safety data are reported up to month 114 for all tofacitinib; efficacy data are reported up to month 96 for tofacitinib 5 mg BID and month 72 for 10 mg BID (with low patient numbers limiting interpretation beyond these time points). Overall, 52% of patients discontinued (24% due to adverse events [AEs] and 4% due to insufficient clinical response); the safety profile remained consistent with that observed in prior phase 1, 2, 3, or LTE studies. The incidence rate (IR; number of patients with events per 100 patient-years) for AEs leading to discontinuation was 6.8. For all-cause AEs of special interest, IRs were 3.4 for herpes zoster, 2.4 for serious infections, 0.8 for malignancies excluding non-melanoma skin cancer, 0.4 for major adverse cardiovascular events, and 0.3 for all-cause mortality. Clinically meaningful improvements in the signs and symptoms of RA and physical functioning, which were observed in the index studies, were maintained.

Conclusions: Tofacitinib 5 mg and 10 mg BID demonstrated a consistent safety profile (as monotherapy or combination therapy) and sustained efficacy in this open-label LTE study of patients with RA. Safety data are reported up to 9.5 years, and efficacy data up to 8 years, based on adequate patient numbers to support conclusions.

Trial registration: NCT00413699, funded by Pfizer Inc (date of trial registration: December 20, 2006)

Keywords: Rheumatoid arthritis, Tofacitinib, Long-term extension

Table 2 Incidence rates for all-cause AEs of special interest *(Continued)*

	All patients (IR (95% CI) [*n*/*N*])		
	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	All tofacitinib
Other			
Composite MACE	0.5 (0.3, 0.7) [20/1046]	0.4 (0.3, 0.5) [42/3358]	0.4 (0.3, 0.5) [62/4404]
Gastrointestinal perforation	0.1 (0.0, 0.2) [3/1123]	0.2 (0.1, 0.3) [20/3358]	0.1 (0.1, 0.2) [23/4481]
Interstitial lung disease	0.2 (0.1, 0.4) [10/1123]	0.2 (0.1, 0.3) [22/3358]	0.2 (0.1, 0.3) [32/4481]
Deep vein thrombosis	0.1 (0.1, 0.3) [6/1123]	0.1 (0.1, 0.2) [17/3358]	0.1 (0.1, 0.2) [23/4481]
Pulmonary embolism	0.1 (0.0, 0.3) [5/1123]	0.1 (0.1, 0.2) [16/3358]	0.1 (0.1, 0.2) [21/4481]

* Correspondence: Lisy.Wang@pfizer.com
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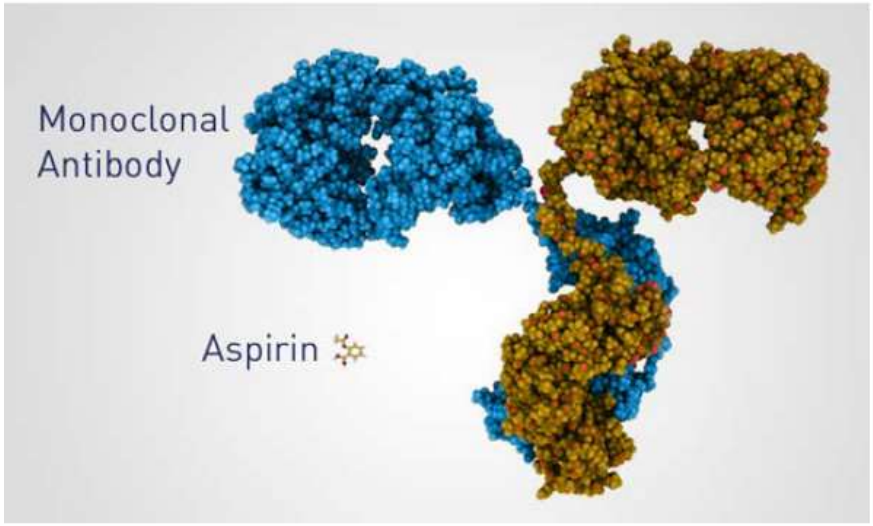
Full list of author information is available at the end of the article

Biosimilar Medications

"A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA approved reference product"



The monoclonal antibody (right) is a large molecule. A single monoclonal antibody weighs more than 800 times what an aspirin molecule (left) weighs.

No difference in purity, chemical identify, pharmacokinetic and pharmacodynamics compared to reference agent

Fda.gov

Biosimilars

Biologic name	Biosimilar
Infliximab (Remicade)	Inflectra, Ixifi, Renflexis
Rituximab (Rituxan)	Ruxience
Adalimumab (Humira)	Amjevita, Cyltezo, Hadlima, Hyrimoz
Etanercept (Enbrel)	Erelzi, Eticovo

Arthritis Care & Research
Vol. 70, No. 10, October 2018, pp 1431–1438
DOI 10.1002/acr.23512

ORIGINAL ARTICLE

Medical Care Costs Associated With Rheumatoid Arthritis in the US: A Systematic Literature Review and Meta-Analysis

ANDREW HRESKO,[1] TZU-CHIEH LIN,[2] AND DANIEL H. SOLOMON[2]

Results. We found 541 potentially relevant studies, and 12 articles met the selection criteria. The quality of studies varied: one-third were poor, one-third were fair, and one-third were good. Total direct medical costs were estimated at $12,509 (95% confidence interval [95% CI] 7,451–21,001) for all RA patients using any treatment regimen and $36,053 (95% CI 32,138–40,445) for bDMARD users. RA-specific costs were $3,723 (95% CI 2,408–5,762) for all RA patients using any treatment regimen and $20,262 (95% CI 17,480–23,487) for bDMARD users.
Conclusion. The total and disease-specific direct medical costs for patients with RA is substantial. Among bDMARD users, the cost of RA care is more than half of all direct medical costs.

Malignancy Risks and Rheumatology

Increased risk of lymphoma in RA patients

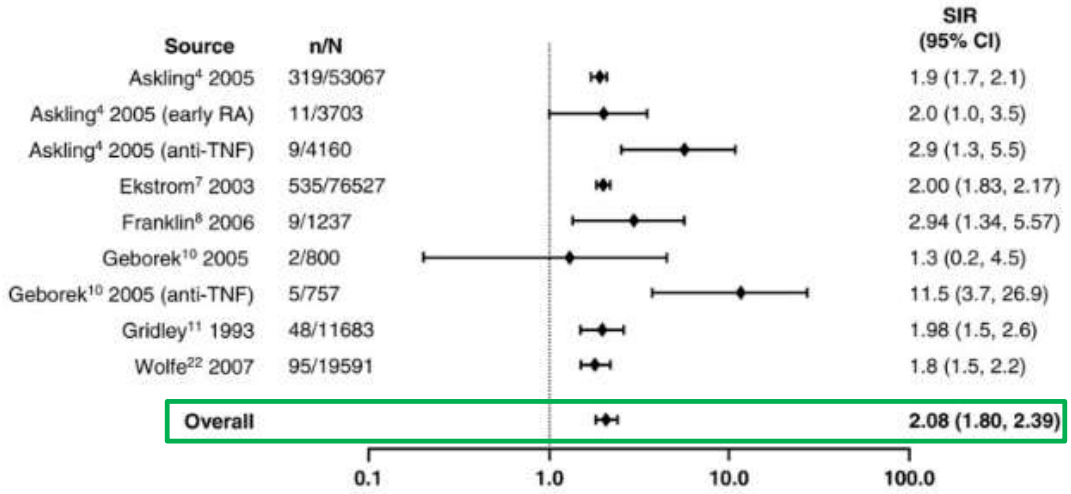


Figure 1

Relative risk of overall lymphoma in patients with rheumatoid arthritis (RA) compared with the general population. CI, confidence interval; n, number of malignancies; N, population size; SIR, standardized incidence ratio; TNF, tumor necrosis factor.

Arthritis Research & Therapy2008**10**:R45

Risks of cancer in RA therapies

Especially biologic medications such as TNFi

Risks of cancer in RA therapies

Risk of Malignancies in Patients With Rheumatoid Arthritis Treated With Biologic Therapy

A Meta-analysis

Maria A. Lopez-Olivo, MD, PhD
Jean H. Tayar, MD
Juan A. Martinez-Lopez, MD
Eduardo N. Pollono, MD
Jose Polo Cueto, MD
M. Rosa Gonzales-Crespo, MD
Stephanie Fulton, MSIS
Maria E. Suarez-Almazor, MD, PhD

Context Concerns exist regarding the potential development of malignancies in patients with rheumatoid arthritis (RA) who are receiving biologic response modifiers (BRMs).

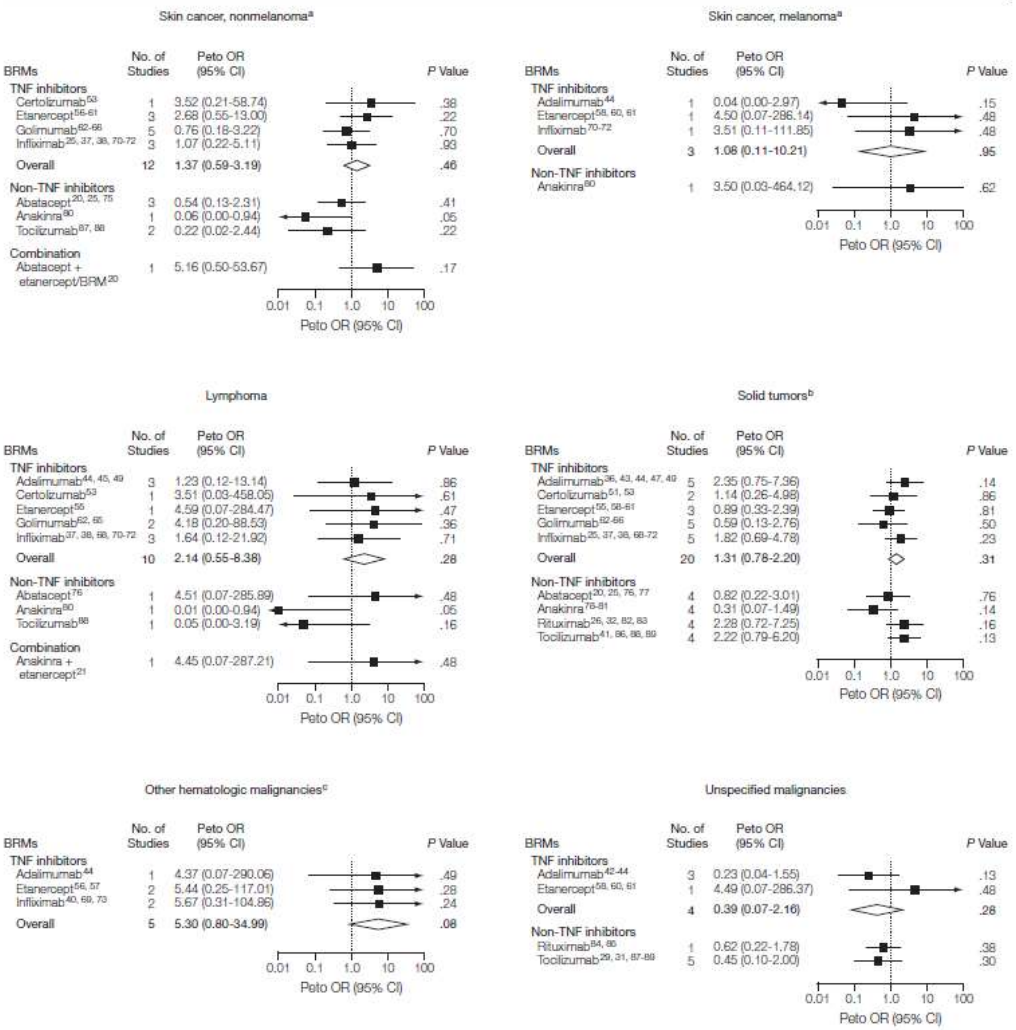
Objective To assess the risk of malignancy in patients with RA enrolled in randomized controlled trials (RCTs) of BRMs.

Data Sources Electronic databases, conference proceedings, and websites of regulatory agencies were searched for RCTs evaluating abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab in RA from inception through July 9, 2012.

Study Selection Independent selection of studies included RCTs that compared the

No significant increased risk in cancer in patients with RA treated with biologics

Figure. Effect of BRMs on Occurrence of Specific Types of Cancer in Patients With Rheumatoid Arthritis



BRM indicates biologic response modifier; OR, odds ratio; TNF, tumor necrosis factor. Numbers of patients included in each comparison are reported in eTable 5. Diamonds represent pooled effect estimates with 95% CIs for all TNF inhibitors.

[a] For infliximab, 1 patient reported both squamous cell carcinoma and melanoma.

[b] Adrenal, bladder, breast, cholangiocarcinoma, fibrosarcoma, gastrointestinal, hepatic, leiomyosarcoma, liposarcoma, lung, ovarian, pancreatic, prostate, renal, testicular, thyroid, tongue, and uterine.

[c] Multiple myeloma and leukemia.

Risks of cancer in RA therapies

JAMA Internal Medicine | Original Investigation

Malignant Neoplasms in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors, Tocilizumab, Abatacept, or Rituximab in Clinical Practice

A Nationwide Cohort Study From Sweden

Hjalmar Wadström, MD; Thomas Frisell, PhD; Johan Askling, MD, PhD; for the Anti-Rheumatic Therapy in Sweden (ARTIS) Study Group

One of the largest observational studies on risk of malignant neoplasms in RA patients to date

Found the overall risk of developing cancer with biologics did not differ from bDMARD naïve RA

TNFi, tocilizumab, abatacept, rituximab were not associated with increased risk of cancer

Exception increased HR for abatacept and squamous cell skin cancers

Table 2. Number of Persons, Events, Crude Incidences, Age- and Sex-Adjusted HRs, and Fully Adjusted HRs for the Different Malignant Neoplasms Under Study in Swedish Cohorts of Patients With RA Initiating Different Antirheumatic Therapies and General Population Comparators

Cohort	Persons at Risk, No.	Events, No.	Crude Incidence per 100 000 Person-years	HR 1 (95% CI)[a]	HR 2 (95% CI)[b]
First Invasive Solid or Hematologic Malignant Neoplasm Excluding NMSC					
Tocilizumab	1693	50	959	0.87 (0.66-1.16)	0.89 (0.67-1.18)
Abatacept	1894	61	1026	0.88 (0.68-1.13)	0.88 (0.68-1.14)
Rituximab	3119	141	1074	0.86 (0.72-1.02)	0.86 (0.73-1.03)
TNFi (first bDMARD)	10 300	478	978	0.92 (0.84-1.01)	0.93 (0.85-1.01)
TNFi (second bDMARD)	4130	169	917	0.88 (0.76-1.03)	0.89 (0.76-1.04)
csDMARD	42 365	3260	1328	1 [Reference]	1 [Reference]
General population	99 609	4193	953	0.90 (0.82-0.99)	NA
First Invasive Solid Malignant Neoplasm Excluding NMSC					
Tocilizumab	1697	47	899	0.92 (0.69-1.23)	0.95 (0.71-1.27)
Abatacept	1900	54	903	0.86 (0.66-1.13)	0.88 (0.67-1.16)
Rituximab	3187	132	985	0.88 (0.74-1.05)	0.90 (0.75-1.08)
First TNFi	10 325	434	884	0.94 (0.85-1.03)	0.94 (0.86-1.04)
TNFi as the second bDMARD	4142	153	827	0.89 (0.76-1.05)	0.91 (0.77-1.07)
csDMARD	42 584	2910	1175	1 [Reference]	1 [Reference]
General population	100 118	3883	877	0.93 (0.84-1.03)	NA
First Invasive Hematologic Malignant Neoplasm					
Tocilizumab	1793	3	54	<5 Events[c]	<5 Events
Abatacept	2014	9	141	1.07 (0.55-2.06)	1.04 (0.53-2.03)
Rituximab	3513	17	114	0.78 (0.48-1.27)	0.74 (0.45-1.22)
First TNFi	10 756	54	104	0.85 (0.65-1.10)	0.85 (0.65-1.10)
TNFi as the second bDMARD	4334	20	102	0.85 (0.54-1.33)	0.84 (0.54-1.32)
csDMARD	46 358	448	164	1 [Reference]	1 [Reference]
General population	106 930	403	84	0.71 (0.59-0.85)	NA
First Invasive Squamous Cell Skin Cancer					
Tocilizumab	1788	5	90	1.16 (0.48-2.80)	0.93 (0.39-2.21)
Abatacept	2016	17	266	2.98 (1.81-4.90)	2.15 (1.31-3.52)
Rituximab	3566	24	159	1.38 (0.90-2.11)	1.01 (0.66-1.55)
First TNFi	10 760	54	104	1.24 (0.95-1.62)	1.09 (0.84-1.42)
TNFi as the second bDMARD	4333	17	86	1.05 (0.66-1.69)	0.86 (0.54-1.39)
csDMARD	46 416	467	171	1 [Reference]	1 [Reference]
General population	107 235	263	55	0.64 (0.46-0.88)	NA
First Invasive Melanoma					
Tocilizumab	1782	3	54	<5 Events	<5 Events
Abatacept	2005	7	110	1.33 (0.61-2.90)	1.43 (0.66-3.09)
Rituximab	3545	9	60	0.69 (0.36-1.35)	0.73 (0.38-1.39)
First TNFi	10 744	32	62	0.85 (0.60-1.18)	0.84 (0.60-1.18)
TNFi as the second bDMARD	4331	13	66	0.92 (0.52-1.61)	0.94 (0.53-1.66)
csDMARD	46 315	234	86	1 [Reference]	1 [Reference]
General population	106 829	290	61	0.84 (0.57-1.23)	NA

Table 2. Number of Persons, Events, Crude Incidences, Age- and Sex-Adjusted HRs, and Fully Adjusted HRs for the Different Malignant Neoplasms Under Study in Swedish Cohorts of Patients With RA Initiating Different Antirheumatic Therapies and General Population Comparators

Cohort	Persons at Risk, No.	Events, No.	Crude Incidence per 100 000 Person-years	HR 1 (95% CI)[a]	HR 2 (95% CI)[b]
First Invasive Solid or Hematologic Malignant Neoplasm Excluding NMSC					
Tocilizumab	1693	50	959	0.87 (0.66-1.16)	0.89 (0.67-1.18)
Abatacept	1894	61	1026	0.88 (0.68-1.13)	0.88 (0.68-1.14)
Rituximab	3119	141	1074	0.86 (0.72-1.02)	0.86 (0.73-1.03)
TNFi (first bDMARD)	10 300	478	978	0.92 (0.84-1.01)	0.93 (0.85-1.01)
TNFi (second bDMARD)	4130	169	917	0.88 (0.76-1.03)	0.89 (0.76-1.04)
csDMARD	42 365	3260	1328	1 [Reference]	1 [Reference]
General population	99 609	4193	953	0.90 (0.82-0.99)	NA
First Invasive Solid Malignant Neoplasm Excluding NMSC					
Tocilizumab	1697	47	899	0.92 (0.69-1.23)	0.95 (0.71-1.27)
Abatacept	1900	54	903	0.86 (0.66-1.13)	0.88 (0.67-1.16)
Rituximab	3187	132	985	0.88 (0.74-1.05)	0.90 (0.75-1.08)
First TNFi	10 325	434	884	0.94 (0.85-1.03)	0.94 (0.86-1.04)
TNFi as the second bDMARD	4142	153	827	0.89 (0.76-1.05)	0.91 (0.77-1.07)
csDMARD	42 584	2910	1175	1 [Reference]	1 [Reference]
General population	100 118	3883	877	0.93 (0.84-1.03)	NA
First Invasive Hematologic Malignant Neoplasm					
Tocilizumab	1793	3	54	<5 Events[c]	<5 Events
Abatacept	2014	9	141	1.07 (0.55-2.06)	1.04 (0.53-2.03)
Rituximab	3513	17	114	0.78 (0.48-1.27)	0.74 (0.45-1.22)
First TNFi	10 756	54	104	0.85 (0.65-1.10)	0.85 (0.65-1.10)
TNFi as the second bDMARD	4334	20	102	0.85 (0.54-1.33)	0.84 (0.54-1.32)
csDMARD	46 358	448	164	1 [Reference]	1 [Reference]
General population	106 930	403	84	0.71 (0.59-0.85)	NA
First Invasive Squamous Cell Skin Cancer					
Tocilizumab	1788	5	90	1.16 (0.48-2.80)	0.93 (0.39-2.21)
Abatacept	2016	17	266	2.98 (1.81-4.90)	2.15 (1.31-3.52)
Rituximab	3566	24	159	1.38 (0.90-2.11)	1.01 (0.66-1.55)
First TNFi	10 760	54	104	1.24 (0.95-1.62)	1.09 (0.84-1.42)
TNFi as the second bDMARD	4333	17	86	1.05 (0.66-1.69)	0.86 (0.54-1.39)
csDMARD	46 416	467	171	1 [Reference]	1 [Reference]
General population	107 235	263	55	0.64 (0.46-0.88)	NA
First Invasive Melanoma					
Tocilizumab	1782	3	54	<5 Events	<5 Events
Abatacept	2005	7	110	1.33 (0.61-2.90)	1.43 (0.66-3.09)
Rituximab	3545	9	60	0.69 (0.36-1.35)	0.73 (0.38-1.39)
First TNFi	10 744	32	62	0.85 (0.60-1.18)	0.84 (0.60-1.18)
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General population	106 829	290	61	0.84 (0.57-1.23)	NA

Risk of Malignancy in Patients Treated with Tofacitinib: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study

Farzin Khosrow-Khavar PhD[1,], Rishi J Desai PhD[1,], Hemin Lee MD MPH[1], Su Been Lee BA[1,], Seoyoung C Kim MD ScD[1,2]

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Background

- Recent results from ORAL Surveillance trial have indicated that tofacitinib, in comparison with tumor necrosis factor inhibitors (TNFI), is associated with increased risk of malignancies in patients with rheumatoid arthritis (RA)
- We conducted a multi-database, population-based study in United States to further examine this safety concern in RA patients treated in setting of routine clinical care

Objective

- To compare the risk of malignancy outcomes between use of tofacitinib and TNFI in RA patients in setting of routine clinical care

Data Sources

- Optum Clinformatics: November 2012-June 2020
- IBM Market Scan: November 2012-December 2018
- Medicare (Parts A,B, D): November 2012-December 2017

Real World Evidence Study Cohort

Inclusion Criteria:
- Patients treated with tofacitinib or TNFI in MarketScan, Optum, and Medicare fee-for-service
- At least 365 days of continuous enrollment in health plan prior to and including cohort entry date
- At least two RA codes between 7 and 365 days apart

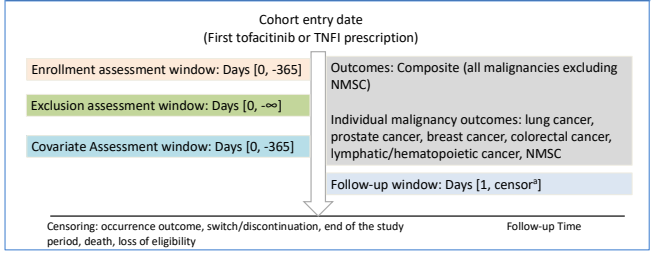
Exclusion Criteria:
- No index drug in the 365 days prior to cohort entry (prevalent users)
- < 18 years of age (Optum, MarketScan), < 65 (Medicare)
- Missing data on age or gender
- Nursing home or hospice admission
- Diagnosis of malignancies, excluding non-melanoma skin cancer (NMSC), prior to cohort entry date
- TNFI users with prior prescriptions of Janus kinase inhibitors (tofacitinib, baricitinib, or upadacitinib)
- TNFI users with prescriptions of multiple TNFI agents on cohort entry date
- Tofacitinib users with prescriptions of baricitinib or upadacitinib on or prior to cohort entry date

RCT-duplicate Study Cohort

Additional Inclusion Criteria:
- At least one prescription of methotrexate
- At least one cardiovascular risk factor (including smoking, hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, family history of ischemic heart disease)

Additional Exclusion Criteria:
- < 50 years of age (Optum, MarketScan), < 65 (Medicare)
- Patients recently hospitalized with infections
- Pregnant patients

Study Design



Methods

Follow-up Scheme:
- As-treated: follow from tofacitinib or TNFI initiation for study outcomes until treatment discontinuation or switch, insurance disenrollment, death, or end of the study period, whichever occurred first

Outcome definition:
- Any new malignancies excluding NMSC: a validated claims-based algorithm with two inpatient or outpatient ICD-9 or ICD-10 diagnosis codes of the same type of malignancy occurring within 60 days

Covariates:
- Demographics, lifestyle variables, RA-related variables, comorbidities, co-medications, markers of healthcare resource utilization

Primary analysis:
- Cox-proportional hazards model to compare risk of malignancies between use of tofacitinib and tamoxifen using propensity score fine-stratification weighting
- Meta-analysis: fixed effects models with inverse variance weighting

Baseline Characteristics

RWE Cohort:
- 83,295 patients: 25,410 in Optum, 29,511 in MarketScan, and 28,374 in Medicare
- 13% in Optum, 15% in MarketScan, 10% in Medicare initiated on tofacitinib
- Mean age in years (tofacitinib users vs TNFI users): 55.9 vs 53.6 in Optum, 53.8 vs 51.6 in MarketScan, and 71.3 vs 71.4 in Medicare
- Majority were female (77- 80%), white (66-83%), had received prior treatment with conventional DMARDs (75- 82%) and glucocorticoids (69-72%)

RCT-Duplicate Cohort:
- 27,035 patients: 5,899 in Optum, 6,588 in MarketScan, 14,548 in Medicare
- 11% in Optum, 14% in MarketScan, and 8% in Medicare initiated on tofacitinib

Primary Analysis

- Incidence rate (tofacitinib vs TNFI) per 100 person-years: 1.68 vs 1.36 in Optum, 0.60 vs 0.86 in MarketScan, 2.70 vs 2.49 in Medicare
- RWE cohort, Pooled Hazard Ratio (95% CI): 1.01 (0.83, 1.22)
- RCT-duplicate cohort, Pooled Hazard Ratio (95% CI): 1.17 (0.85, 1.62)

Secondary Analyses: RWE Cohort

Individual Cancer Endpoints (HR, 95% CI):
- Lung Cancer: 1.20 (0.77, 1.87)
- Breast Cancer: 0.85 (0.53, 1.38)
- Prostate Cancer: 0.92 (0.51, 1.67)
- Colorectal Cancer: 0.71 (0.33, 1.56)
- Blood cancers: 0.91 (0.53, 1.58)
- NMSC: 1.15 (0.96, 1.39)

Subgroup Analyses (HR, 95% CI):
- Female: 0.93 (0.73, 1.18)
- Male: 1.21 (0.86, 1.71)
- Age ≤ 65: 0.89 (0.63, 1.24)
- Age > 65: 1.08 (0.85, 1.37)
- Previous bMARD: 0.81 (0.60, 1.10)
- No previous bDMARD: 1.22 (0.96, 1.57)

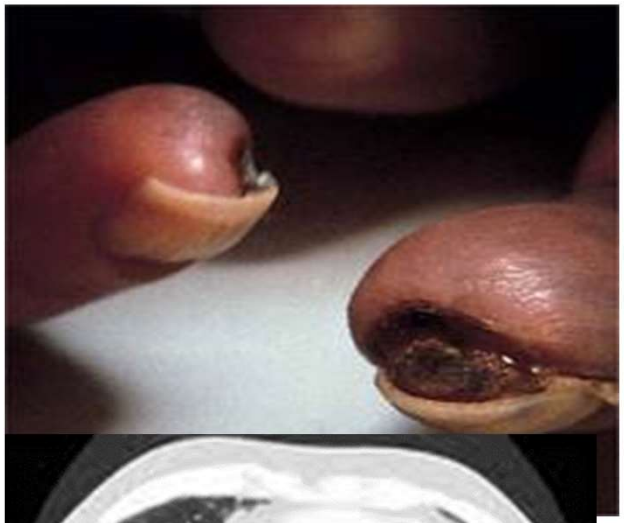
Conclusions

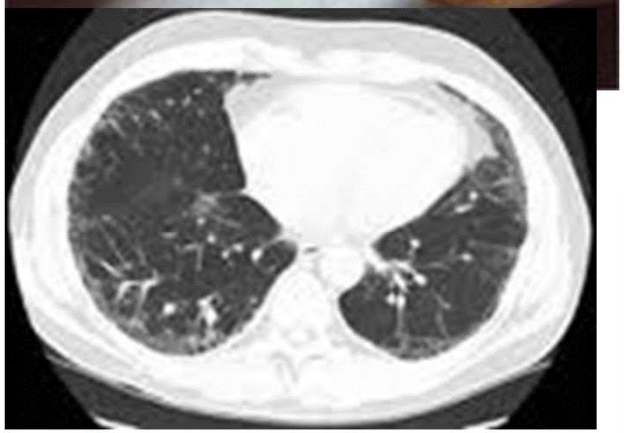
- In this population-based study, no evidence of increased risk of malignancies with tofacitinib, in comparison with TNFI, in all RA patients treated in real-world setting
- An increased risk of malignancies cannot be ruled out with tofacitinib in older patients and with longer treatment duration

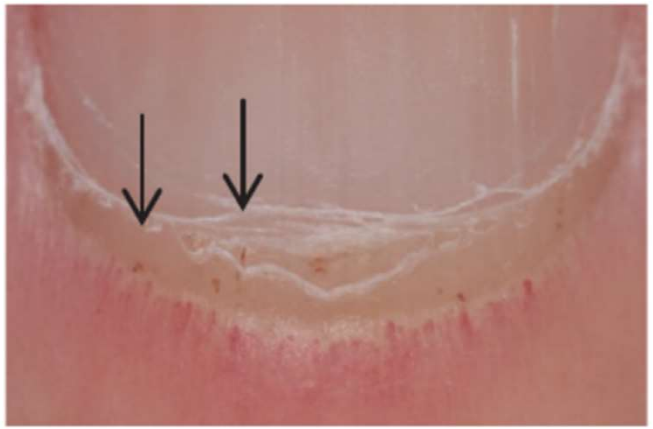
Disclosures and Acknowledgements

- SCK has received research grants to the Brigham and Women's Hospital from Roche/Genentech, Pfizer, Bristol-Myers Squibb, Roche, and AbbVie for unrelated studies. RJD has received research grants to the Brigham and Women's Hospital from Bayer, Novartis, and Vertex for unrelated projects. All other authors have no conflict of interests to disclose
- This study was funded by internal sources of the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital & Harvard Medical School. SCK is supported by the National Institutes of Health (NIH) grant -K24AR078959. FK is supported by a postdoctoral fellowship from Fonds de recherche du Québec-Santé

Systemic Sclerosis







1. Nailfold bleeding.

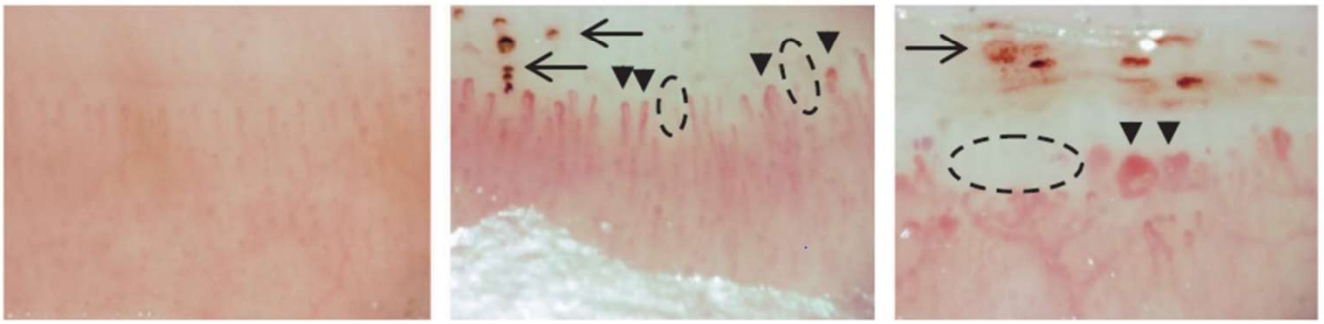


Figure 2. Capillaroscopy imaging.

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Table 1: The ACR/EULAR Criteria for the Classification of SSc*

Item	Sub-item(s)	Weight/ score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (*sufficient criterion*)	-	9
Skin thickening of the fingers (*only count the higher score*)	Puffy fingers Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions (*only count the higher score*)	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/ or interstitial lung disease (*maximum score is 2*)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	-	3
Scleroderma-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) (*maximum score is 3*)	Anticentromere Anti–topoisomerase I Anti–RNA polymerase III	3

* These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiropathy).

† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of >9 are classified as having definite systemic sclerosis.

Credit: Arthritis Rheum. *2013;65:2737-2747.*

Sensitivity 91%

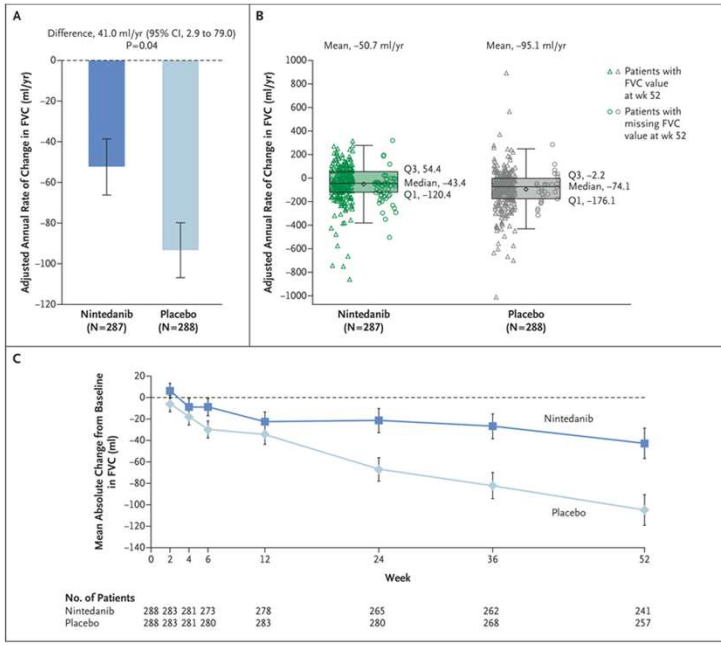
Specificity 92%

ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Oliver Distler, M.D., Kristin B. Highland, M.D., Martina Gahlemann, M.D., Arata Azuma, M.D., Aryeh Fischer, M.D., Maureen D. Mayes, M.D., Ganesh Raghu, M.D., Wiebke Sauter, Ph.D., Mannaig Girard, M.Sc., Margarida Alves, M.D., Emmanuelle Clerisme-Beaty, M.D., Susanne Stowasser, M.D., et al., for the SENSCIS Trial Investigators*

June 27, 2019
N Engl J Med 2019; 380:2518-2528
DOI: 10.1056/NEJMoa1903076



Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis and a leading cause of systemic sclerosis-related death.

Nintedanib, a tyrosine kinase inhibitor, has been shown to have antifibrotic and anti-inflammatory effects in preclinical models of systemic sclerosis and ILD.

On the basis of evidence from two randomized, double-blind trials (Scleroderma Lung Studies I and II [SLS-I and SLS-II]), the immunosuppressants mycophenolate and cyclophosphamide are frequently used for the treatment of ILD associated with systemic sclerosis. In addition, targeted treatments are licensed to address other organ manifestations such as pulmonary arterial hypertension and digital ulcers.

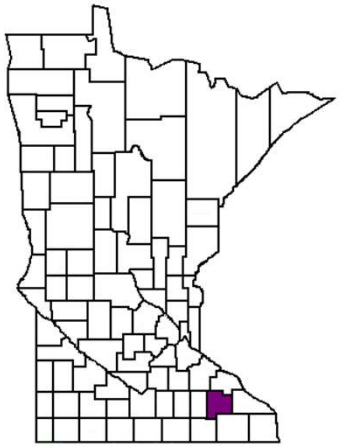
Among patients with ILD associated with systemic sclerosis, the annual rate of decline in FVC was lower with nintedanib than with placebo; no clinical benefit of nintedanib was observed for other manifestations of systemic sclerosis.

The adverse-event profile of nintedanib observed in this trial was similar to that observed in patients with idiopathic pulmonary fibrosis; gastrointestinal adverse events, including diarrhea, were more common with nintedanib than with placebo

Giant Cell Arteritis

A rare but serious autoimmune disease involving inflammation of large blood vessels including the aorta and carotid arteries

- **Epidemiology**
  - US Lifetime risk: 1% women 0.5% men
  - Highest incidence in Scandinavia (Olmsted County, MN: 17/100,000 persons over age 50)
  - Unusual in Latinos, Asians, and Arabs. Extremely uncommon in African-Americans.
  - Greatest risk factor: aging. Almost NEVER occurs before age 50
  - Peak onset between ages 70-79 with >80% of patients over 70 years of age (mean age 76.7 years)



Clinical Manifestations of GCA

PMR symptoms (seen in 40-50% of patients with GCA)

Constitutional symptoms are common

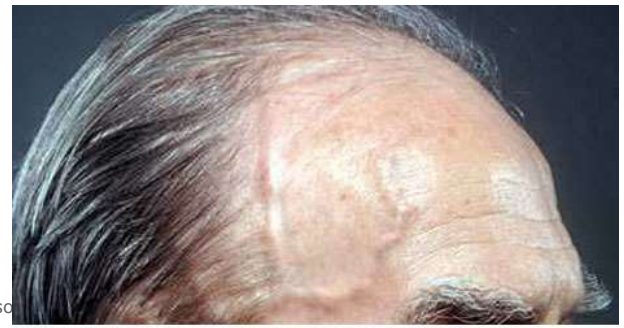
- Fever, fatigue, weight loss
- 50% of patients can have fevers

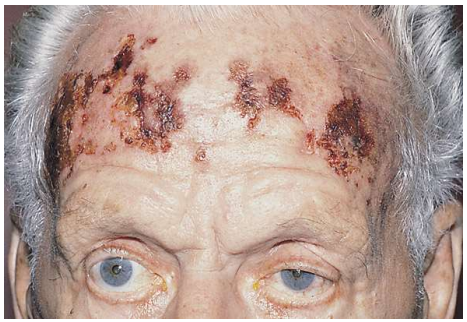
Headaches are seen in 2/3 of GCA patients

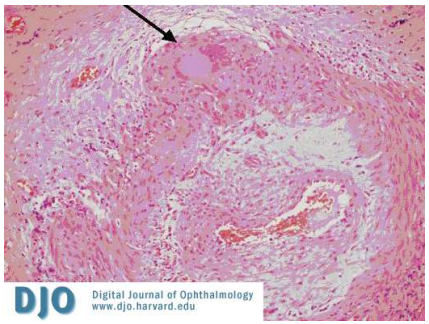
- Most commonly temporal, but can be occipital, frontal, other locations
- New and improves with steroid treatment

Jaw claudication seen in ½ of GCA patients

- Rapid onset with chewing and severe jaw pain (can occur with repeated swallowing and in the tongue with eating)
- Highly associated with a positive temporal artery biopsy



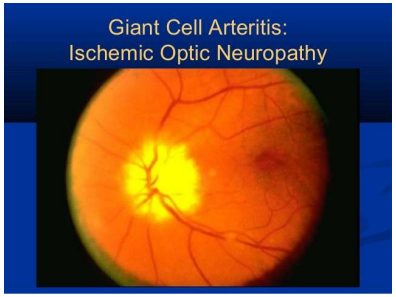




Clinical Manifestations of GCA

Vision loss

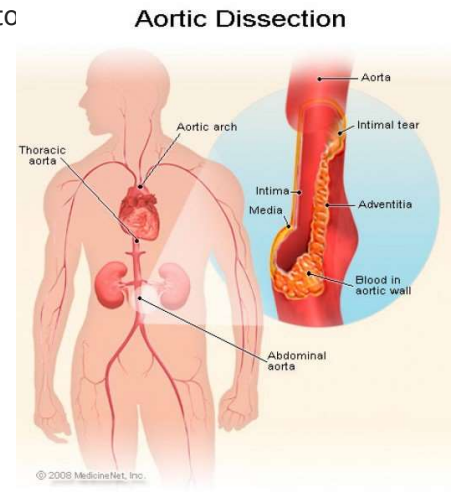
- Transient monocular impairment (amaurosis fugax)
- Permanent – highest risk early/prior to steroid initiation
- If one eye affected and no treatment- further loss of 25-50% patients
  - Anterior ischemic optic neuropathy, Central retinal artery occlusion, posterior ischemic optic neuropathy, branch retinal artery occlusion, cerebral ischemia



Aortitis

- More common in thoracic versus abdominal aorta
- 10-20% patients will have aortic aneurism
  - Small studies using CT-angiography have found evidence of aortitis in up to 60% of newly diagnosed patients
  - Mayo data: GCA patients 17 times more likely to develop thoracic aortic aneurysms and 2.4 times more likely to develop isolated abdominal aortic aneurysms compared to persons of the same age and sex

Stroke and aortic dissection: rare in newly diagnosed patients: <5% of cases



2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR **GIANT CELL ARTERITIS**

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of large-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CRITERIA ABSOLUTE REQUIREMENTS

Age ≥ 50 years at time of diagnosis	

ADDITIONAL CLINICAL CRITERIA

Morning stiffness in shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery[1]	+2

LABORATORY, IMAGING, AND BIOPSY CRITERIA

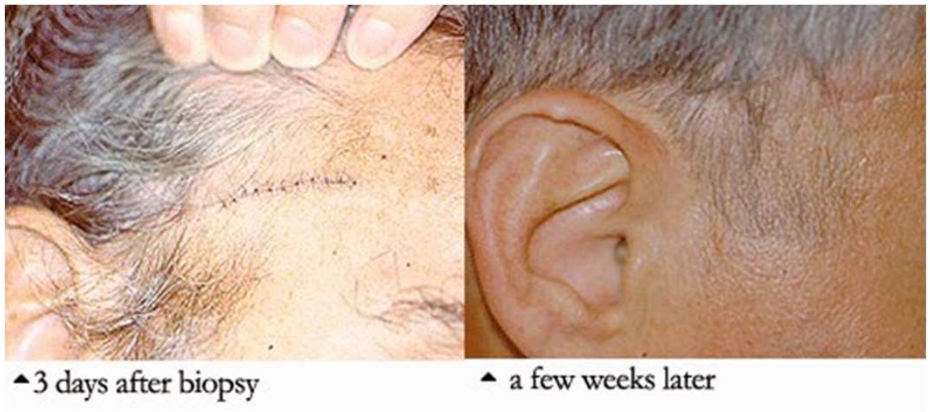
Maximum ESR ≥ 50 mm/hour or maximum CRP ≥ 10 mg/liter[2]	+2
Positive temporal artery biopsy or halo sign on temporal artery ultrasound[3]	+5
Bilateral axillary involvement[4]	+2
FDG-PET activity throughout aorta[5]	+2

Sum the scores for 10 items, if present. A score of ≥ 6 points is needed for the classification of GIANT CELL ARTERITIS.

Sensitivity 87%
Specificity 95%

GCA Diagnosis and Treatment

Labs: CBC, BMP, LFTs, ESR, CRP, albumin. Consider work-up for other autoimmune diseases if inflammatory arthritis
Temporal artery **biopsy**: obtain within 3 weeks of steroids



Treatment: prednisone 1 mg/kg immediately. Pulse dose steroids (1g IV x 3 days if vision loss, stroke, or aortic dissection)

Refer to rheumatology

For decades, we have used prednisone and other steroid treatments for management of this disease

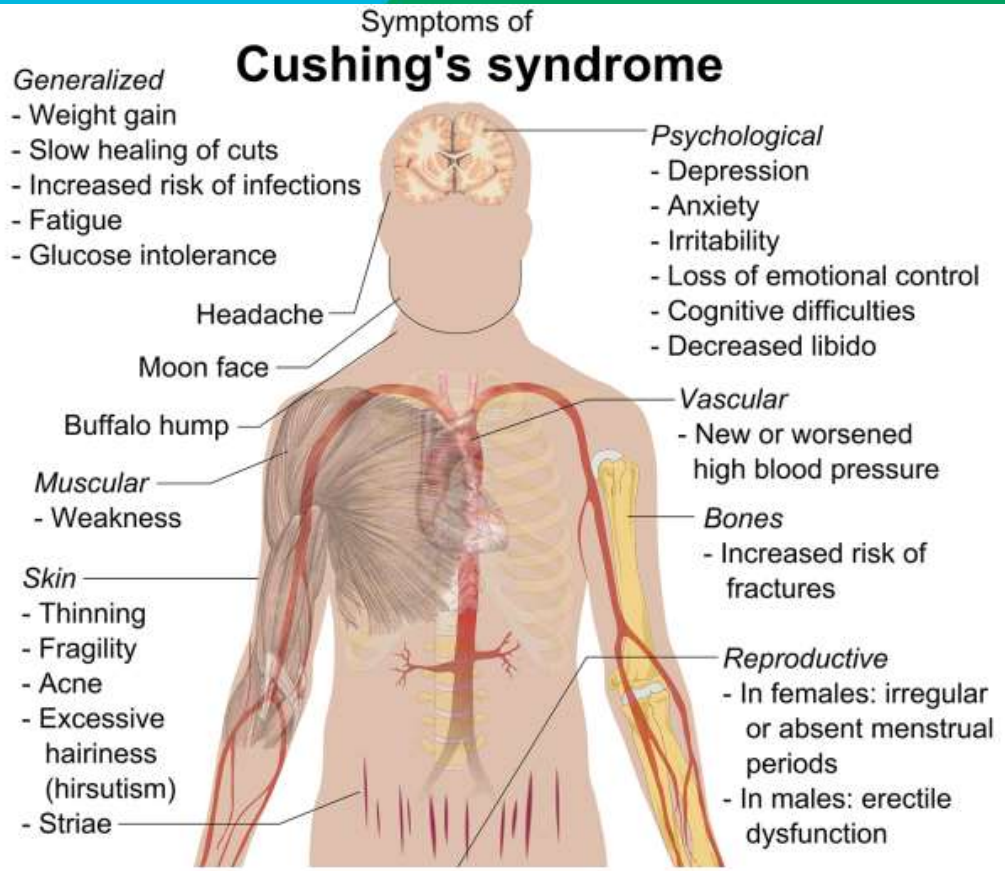
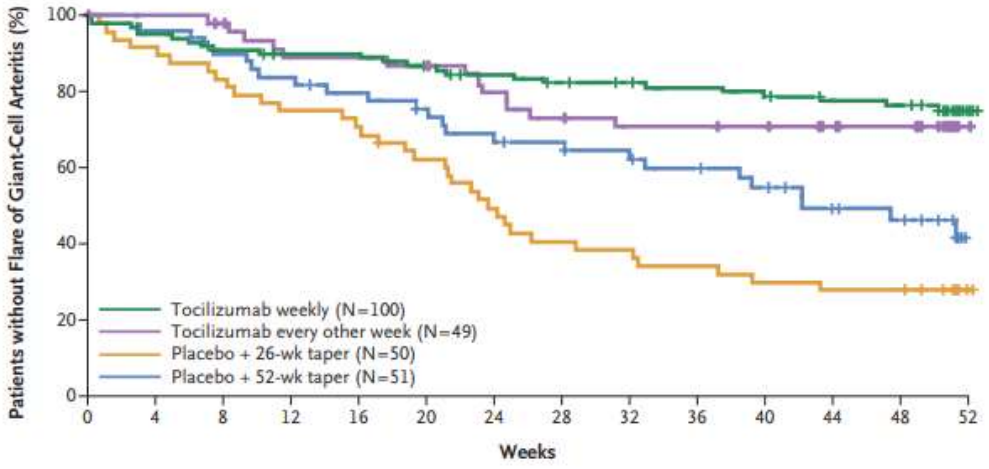


Figure 4. Symptoms of Cushing's Syndrome, or chronic systemic effects of elevated glucocorticoids. (Figure by Mikael Häggström, reproduced from Wikimedia Commons)

The NEW ENGLAND JOURNAL of MEDICINE



No. at Risk

Tocilizumab weekly	100	93	88	85	85	81	77	74	71	69	67	64	63	5
Tocilizumab every other week	49	47	45	40	40	39	35	32	30	30	29	26	24	2
Placebo + 26-wk taper	50	44	40	36	34	29	23	19	18	16	14	13	13	3
Placebo + 52-wk taper	51	48	44	41	38	35	32	30	28	25	22	17	15	0

Figure 2. Time to First Flare after Clinical Remission of Giant-Cell Arteritis in All Patients.

Patients who never had remission were considered to have had a flare at week 0 (data were censored [tick marks] at that time point). Patients who withdrew from the trial before week 52 had their data censored at the time of withdrawal. The values at week 52 represent patients without flare whose week 52 visit was on day 364 of the trial only for the purpose of plotting time points; the analysis captured all the trial days associated with a week 52 visit, and appropriate censoring was applied. In a comparison with the placebo group that underwent the 26-week taper, the hazard ratio in the group that received tocilizumab weekly was 0.23 (99% CI, 0.11 to 0.46) and the hazard ratio in the group that received tocilizumab every other week was 0.28 (99% CI, 0.12 to 0.66; P<0.001 for both comparisons). Absolute values for the two tocilizumab groups could not be evaluated because the median was not reached.

Long-term Considerations with Steroid Therapy

- High risk of osteoporosis with GCA dosing of prednisone and steroid taper. Begin calcium, vitamin D (goal 30-60), alendronate or Reclast infusion for bone ppx.
- Begin PPI for GI ppx while on prednisone.
- Close ophthalmology follow-up for glaucoma or cataracts.
- Close PCP follow-up for hypertension, glycemic control, and lipid management.
- Monitor closely for adrenal insufficiency once on prednisone <10 mg/daily.

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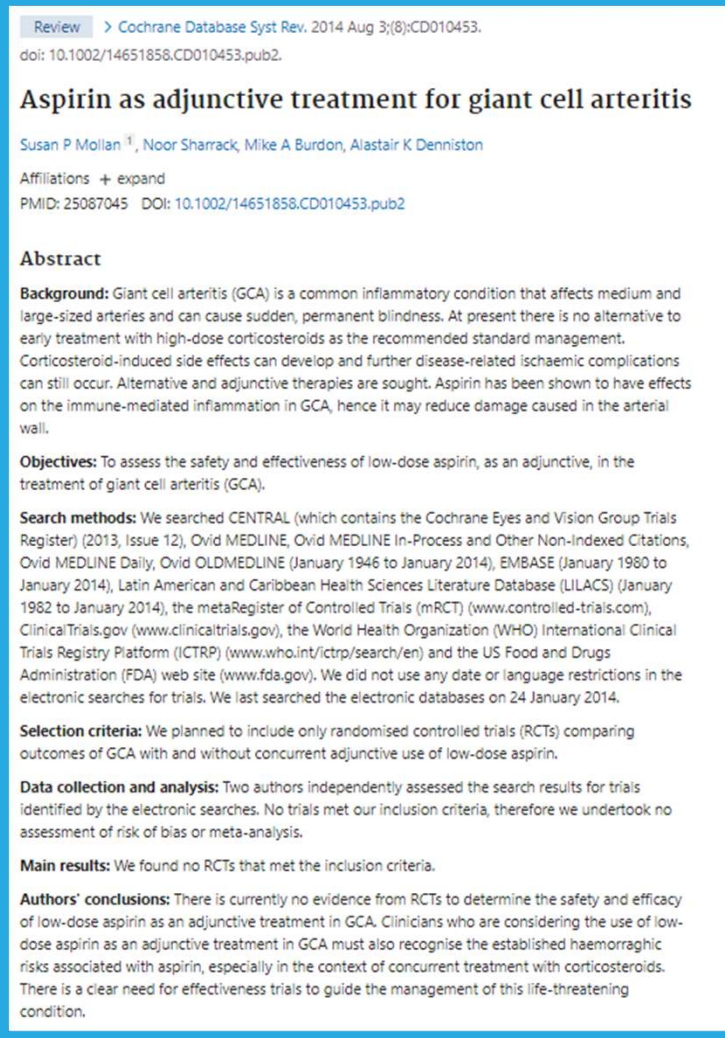


Review > Cochrane Database Syst Rev. 2014 Aug 3;(8):CD010453.
doi: 10.1002/14651858.CD010453.pub2.

Aspirin as adjunctive treatment for giant cell arteritis

Susan P Mollan [1], Noor Sharrack, Mike A Burdon, Alastair K Denniston

Affiliations + expand

PMID: 25087045 DOI: 10.1002/14651858.CD010453.pub2

Abstract

Background: Giant cell arteritis (GCA) is a common inflammatory condition that affects medium and large-sized arteries and can cause sudden, permanent blindness. At present there is no alternative to early treatment with high-dose corticosteroids as the recommended standard management. Corticosteroid-induced side effects can develop and further disease-related ischaemic complications can still occur. Alternative and adjunctive therapies are sought. Aspirin has been shown to have effects on the immune-mediated inflammation in GCA, hence it may reduce damage caused in the arterial wall.

Objectives: To assess the safety and effectiveness of low-dose aspirin, as an adjunctive, in the treatment of giant cell arteritis (GCA).

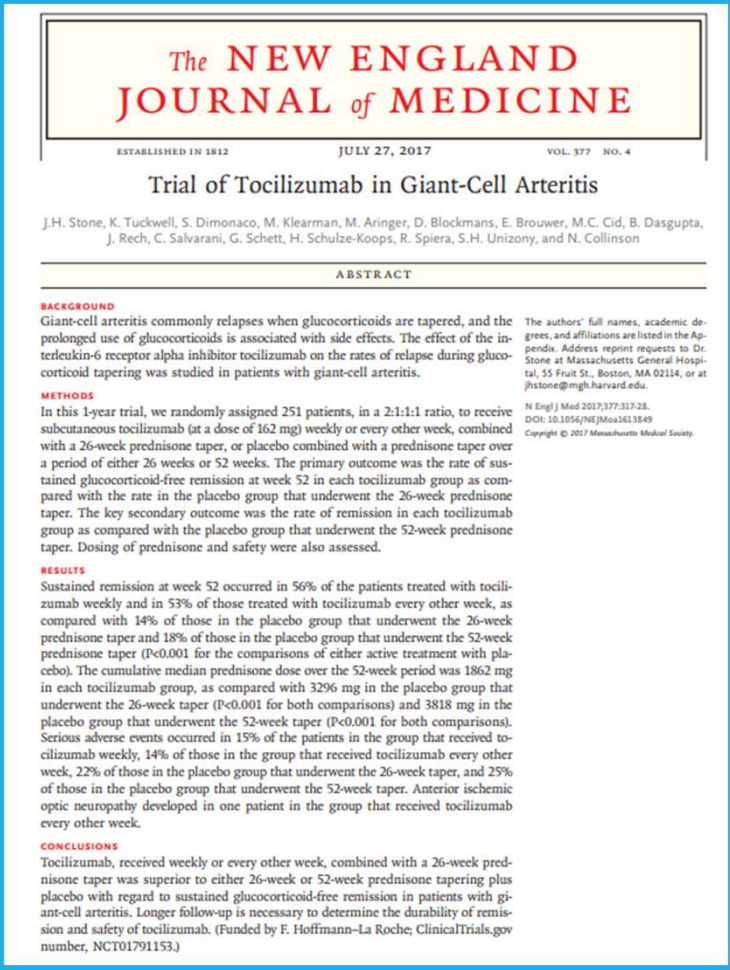
Search methods: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2013, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2014), EMBASE (January 1980 to January 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to January 2014), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) and the US Food and Drugs Administration (FDA) web site (www.fda.gov). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 24 January 2014.

Selection criteria: We planned to include only randomised controlled trials (RCTs) comparing outcomes of GCA with and without concurrent adjunctive use of low-dose aspirin.

Data collection and analysis: Two authors independently assessed the search results for trials identified by the electronic searches. No trials met our inclusion criteria, therefore we undertook no assessment of risk of bias or meta-analysis.

Main results: We found no RCTs that met the inclusion criteria.

Authors' conclusions: There is currently no evidence from RCTs to determine the safety and efficacy of low-dose aspirin as an adjunctive treatment in GCA. Clinicians who are considering the use of low-dose aspirin as an adjunctive treatment in GCA must also recognise the established haemorrhagic risks associated with aspirin, especially in the context of concurrent treatment with corticosteroids. There is a clear need for effectiveness trials to guide the management of this life-threatening condition.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 27, 2017 VOL. 377 NO. 4

Trial of Tocilizumab in Giant-Cell Arteritis

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ABSTRACT

BACKGROUND

Giant-cell arteritis commonly relapses when glucocorticoids are tapered, and the prolonged use of glucocorticoids is associated with side effects. The effect of the interleukin-6 receptor alpha inhibitor tocilizumab on the rates of relapse during glucocorticoid tapering was studied in patients with giant-cell arteritis.

METHODS

In this 1-year trial, we randomly assigned 251 patients, in a 2:1:1:1 ratio, to receive subcutaneous tocilizumab (at a dose of 162 mg) weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. The primary outcome was the rate of sustained glucocorticoid-free remission at week 52 in each tocilizumab group as compared with the rate in the placebo group that underwent the 26-week prednisone taper. The key secondary outcome was the rate of remission in each tocilizumab group as compared with the placebo group that underwent the 52-week prednisone taper. Dosing of prednisone and safety were also assessed.

RESULTS

Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly and in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group that underwent the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper ($P<0.001$ for the comparisons of either active treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each tocilizumab group, as compared with 3296 mg in the placebo group that underwent the 26-week taper ($P<0.001$ for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper ($P<0.001$ for both comparisons). Serious adverse events occurred in 15% of the patients in the group that received tocilizumab weekly, 14% of those in the group that received tocilizumab every other week, 22% of those in the placebo group that underwent the 26-week taper, and 25% of those in the placebo group that underwent the 52-week taper. Anterior ischemic optic neuropathy developed in one patient in the group that received tocilizumab every other week.

CONCLUSIONS

Tocilizumab, received weekly or every other week, combined with a 26-week prednisone taper was superior to either 26-week or 52-week prednisone tapering plus placebo with regard to sustained glucocorticoid-free remission in patients with giant-cell arteritis. Longer follow-up is necessary to determine the durability of remission and safety of tocilizumab. (Funded by F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT01791153.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Stone at Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, or at jhstone@mgh.harvard.edu.

N Engl J Med 2017;377:317-28.
DOI: 10.1056/NEJMoa1613849

Role of Tocilizumab (IL-6 blockade)

- GiACTA trial - Based on 52-week trial in a double-blind placebo-controlled study with 251 patients with biopsy-proven giant cell arteritis, tocilizumab 162 mg subcutaneous injection weekly was approved by the FDA for the treatment of giant cell arteritis.

- Smaller studies have shown efficacy of IV tocilizumab monthly therapy as well for giant cell arteritis, and infusion treatment might be a consideration in patients unable to obtain insurance coverage for subcutaneous tocilizumab or who cannot tolerate subcutaneous formulation.

- While tocilizumab has been shown to reduce overall prednisone intake, patients should still begin prednisone 1 mg/kg and proceed for temporal artery biopsy if there is clinical suspicion for giant cell arteritis.

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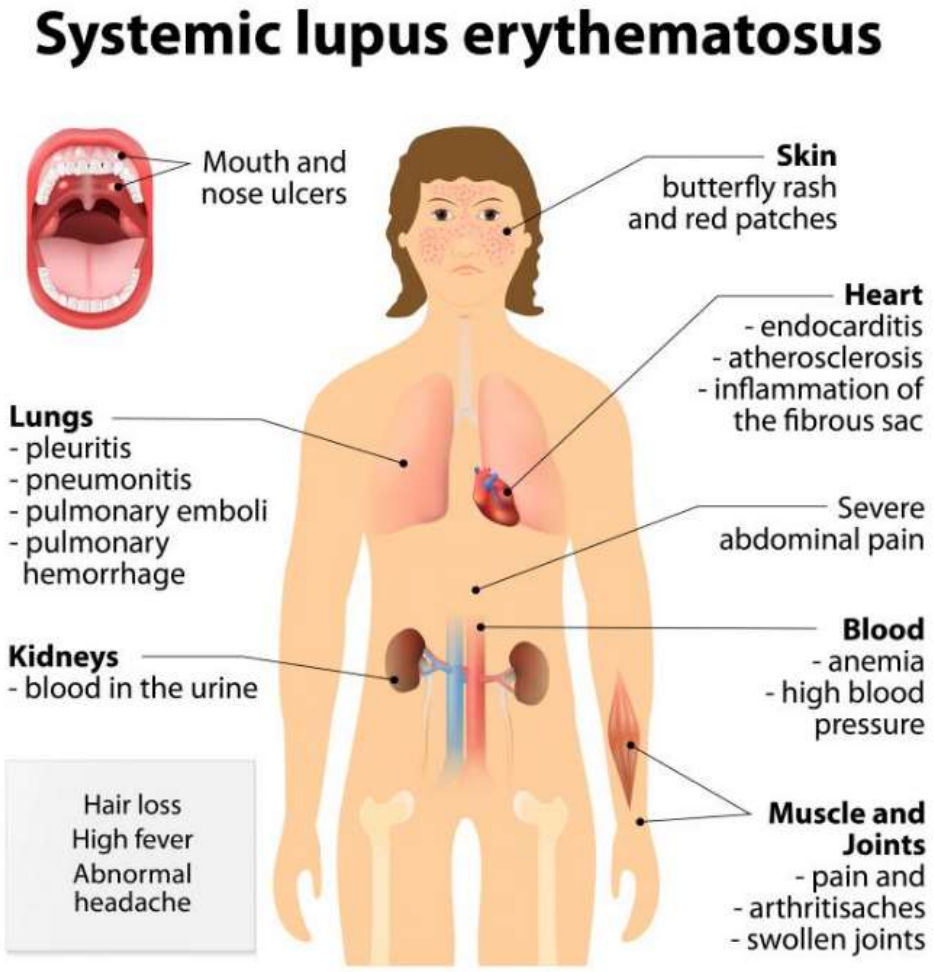
Key Points on Giant Cell Arteritis

• GCA (or temporal arteritis) is a large vessel vasculitis involving any branch of the aorta. Classic symptoms include new or changing headaches, jaw or upper extremity claudication, scalp tenderness, vision changes, fevers, chills, night sweats, or fatigue.

• While steroids are first-line therapy for both PMR and GCA, anti-IL-6 therapy with tocilizumab has been FDA-approved for treatment of giant cell arteritis.

Systemic Lupus Erythematous Updates



Clinical Case

26 year old woman with hypothyroidism presents with joint pain, fatigue, and hair loss

Medications: fluoxetine, OCP

Exam: swelling of wrist and ankle joints, non-scarring alopecia, ulcer on hard palate

Labs: CBC: 3.1 / 12.5 / 129

CMP notable for albumin 3.0

ESR: 43 CRP: <3

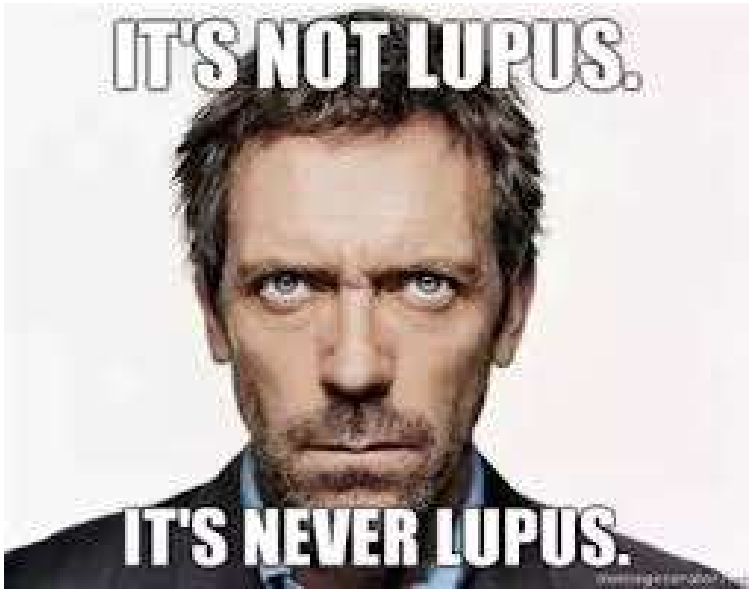
TSH: 3.95

ANA: 1:160 (homogenous), ds-DNA: 300, + SSA >8.0

APS negative, Coombs negative

Urinalysis with normal limits, low C3, normal C4

Does this woman have SLE?



What Is Systemic Lupus Erythematosus?

Systemic lupus erythematosus (SLE) is a progressive chronic autoimmune disease that results in inflammation and tissue damage

Characterized by flares, spontaneous remission, and relapses

SLE can affect any part of the body but often results in damage to the skin, joints, heart, kidneys, lungs, and nervous system

Slide courtesy of Dr. Daniel J. Wallace, MD (UCLA): Disorders that overlap with scleroderma

Diagnostic versus Classification Criteria

Diagnostic criteria

Diagnosis may be defined as the determination of the cause or nature of an illness by evaluation of the signs, symptoms and supportive tests in an individual patient. **Diagnostic criteria are a set of signs, symptoms, and tests for use in routine clinical care to guide the care of individual patients.**

Diagnostic criteria are generally broad and must reflect the different features of a disease (heterogeneity), with a view to accurately identify as many people with the condition as possible. Given this complexity, the development and validation of diagnostic criteria can be quite challenging. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is likely the best-known example of diagnostic criteria. Its initial development was prompted by the observation of extremely poor agreement among providers regarding patients' psychiatric diagnoses. **There are only a few validated diagnostic criteria in rheumatology, and clinicians commonly establish a diagnosis based on subjective combination of clinical signs/symptoms, available clinical tests, and knowledge about the epidemiology of their geographical area.**

Classification criteria

Classification criteria are standardized definitions that are primarily intended to create well-defined, relatively homogenous cohorts for clinical research; they are not intended to capture the entire universe of possible patients, but rather to capture the majority of patients with key shared features of the condition. Hence the goal of classification differs from the intent of diagnostic criteria. Validated classification criteria are considered critical to the interpretation of study findings and comparisons of results between studies. Despite facilitating the comparison of study results, classification criteria have the potential to restrict the external validity of studies, as interventions may perform differently in the study participants who fulfill classification criteria for a disease than in the broader group of persons having been diagnosed with the same disease, i.e., those that share only some but not other disease manifestations considered in classification criteria.

Aggarwal R, et al. Arthritis Care Res (Hoboken). 2015 Jul; 67(7): 891–897.

Systemic Lupus Erythematous Updates

SLICC CRITERIA FOR SLE: 2012

≥4 out of 17 criteria (≥1 clinical and ≥ 1 immunologic) = classify as SLE

CLINICAL

- **SKIN**
  - Acute cutaneous LE
  - Chronic cutaneous LE
- **ORAL ULCERS**
- **ALOPECIA**
- **SYNOVITIS**
- **SEROSITIS**
- **RENAL**
  - Prot/Cr ≥0.5
  - RBC casts
  - ***BIOPSY*******
- **NEUROLOGIC**
  - Sz, psychosis, mononeuritis, myelitis, p or c neuropathy, acute confusional state
- **HEMOLYTIC ANEMIA**
- **LEUKOPENIA** (<4000) or **LYMPHOPENIA** (<1000)
- **THROMBOCYTOPENIA** (100k)

- **IMMUNOLOGIC**
  - **ANA** > normal value
  - **ANTI-dsDNA**
  - **ANTI-Sm**
  - **ANTI-PHOSPHOLIPID**
  - **LOW COMPLEMENT**
  - **DIRECT COOMB'S POS**

93% specificity; 92% sensitivity

Petri M et al for SLICC, Arthritis Rheum 2012

2019 ACR/EULAR Classification criteria for systemic lupus erythematosus

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Martin Aringer et al. Ann Rheum Dis 2019;78:1151-1159

ARD

Clinical criteria	
Acute cutaneous lupus	Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermatomyositis); **OR** subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
Chronic cutaneous lupus	Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chilblains lupus; **OR** discoid lupus/lichen planus overlap
Nonscarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes, such as alopecia areata, drugs, iron deficiency, and androgenic alopecia)
Oral or nasal ulcers	Palate, buccal, tongue, **OR** nasal ulcers (in the absence of other causes, such as vasculitis, Behçet's disease, infection [herpesvirus], inflammatory bowel disease, reactive arthritis, and acidic foods)
Joint disease	Synovitis involving two or more joints, characterized by swelling or effusion **OR**
	Tenderness in two or more joints and at least 30 minutes of morning stiffness
Serositis	Typical pleurisy for more than one day, pleural effusions, or pleural rub, **OR**
	Typical pericardial pain (pain with recumbency improved by sitting forward) for more than one day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler's syndrome
Renal	Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours, **OR**
	Red blood cell casts
Neurologic	Seizures; psychosis; mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes, such as primary vasculitis, infection, and diabetes mellitus); **OR** acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)
Hemolytic anemia	Hemolytic anemia
Leukopenia or lymphopenia	Leukopenia (<4000/mm^3 at least once) (in the absence of other known causes, such as Felty's syndrome, drugs, and portal hypertension), **OR**
	Lymphopenia (<1000/mm^3 at least once) (in the absence of other known causes, such as glucocorticoids, drugs, and infection)
Thrombocytopenia	Thrombocytopenia (<100,000/mm^3) at least once in the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

SLICC criteria for the classification of systemic lupus erythematosus[3]

(4 of 17 criteria, including at least one clinical criterion and one immunologic criterion;¶ **OR** biopsy-proven lupus nephritis[Δ])

Criterion	Definition
Immunologic criteria	
ANA	ANA level above laboratory reference range
Anti-dsDNA	Anti-dsDNA antibody level above laboratory reference range (or >twofold the reference range if tested by ELISA)
Anti-Sm	Presence of antibody to Sm nuclear antigen
Antiphospholipid	Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti-beta 2-glycoprotein I (IgA, IgG, or IgM)
Low complement	Low C3; low C4; **OR** low CH50
Direct Coombs' test	Direct Coombs' test in the absence of hemolytic anemia

Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64:2677.

What is ANA?

Discussing the role of ANA with patients

Mayo Clinic Website: "An ANA test detects antinuclear antibodies (ANA) in your blood. Your immune system normally makes antibodies to help you fight infection. In contrast, antinuclear antibodies often attack your body's own tissues — specifically targeting each cell's nucleus. In most cases, a positive ANA test indicates that your immune system has launched a misdirected attack on your own tissue — in other words, an autoimmune reaction. But some people have positive ANA tests even when they're healthy. Your doctor is likely to order an ANA test for a suspected autoimmune disease such as lupus, rheumatoid arthritis or scleroderma."

ANA is positive in many medical conditions including SLE, systemic sclerosis, rheumatoid arthritis, most patients with Hashimoto's thyroiditis

Up to 1:5 healthy women might have an ANA 1:40; less than 5% of healthy women have an ANA 1:160. ANA is more likely to be positive with aging and more likely to be positive in patients with family members with autoimmune disease

ABIM Choose Wisely (2013)

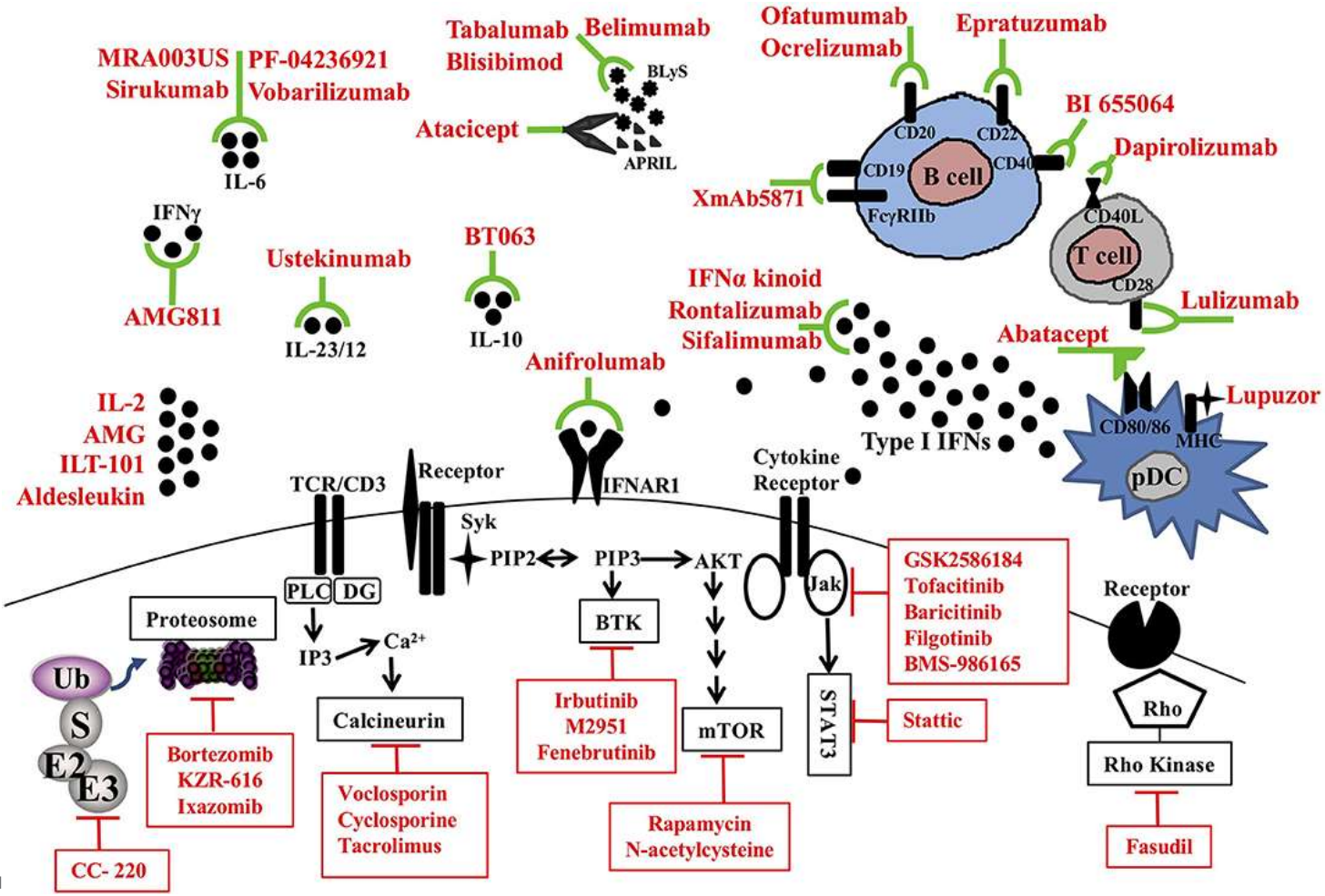
Don't test ANA sub-serologies without a positive ANA and clinical suspicion of immune-mediated disease.

Tests for anti-nuclear antibody (ANA) sub-serologies (including antibodies to double-stranded DNA, Smith, RNP, SSA, SSB, Scl-70, centromere) are usually negative if the ANA is negative.

Exceptions include anti-Jo1, which can be positive in some forms of myositis, or occasionally, anti-SSA, in the setting of lupus or Sjögren's syndrome.

Broad testing of autoantibodies should be avoided; instead the choice of autoantibodies should be guided by the specific disease under consideration.

SLE Treatment Update



Annual Costs of SLE-related Medications (2015)

HCQ	$ 1,080
Prednisone	$ 156
Methotrexate	$ 408
Azathioprine	$ 1,560
Mycophenolate	$ 5,668
Belimumab	$41,760 (w/o infusion costs)

Hahn BH, data from Epocrates Oct 2015, based on www.goodrx.com

Summary on SLE

Order an ANA when you have clinical suspicion that there is an autoimmune disease

Try to avoid extensive lab testing for ENAs (extractable nuclear antibodies) when the ANA screen is negative

An ANA 1:160 is borderline positives and values that are lower are unlikely to be of clinical utility

2019 SLICC criteria are classification criteria meant for research purposes, not diagnostic criteria

Inflammatory Arthritis Order Set

Early rheumatoid arthritis may be difficult to distinguish from other types of inflammatory or non-inflammatory arthritis

Patients are often scared to present to their primary care providers due to fear of disease diagnosis and unwillingness to begin DMARD therapy

Joint manifestations such as erosions on imaging, rheumatoid nodules, and extra-articular manifestations are typically seen in patients with years of poorly-controlled disease. These tend to be absent in early rheumatoid arthritis.

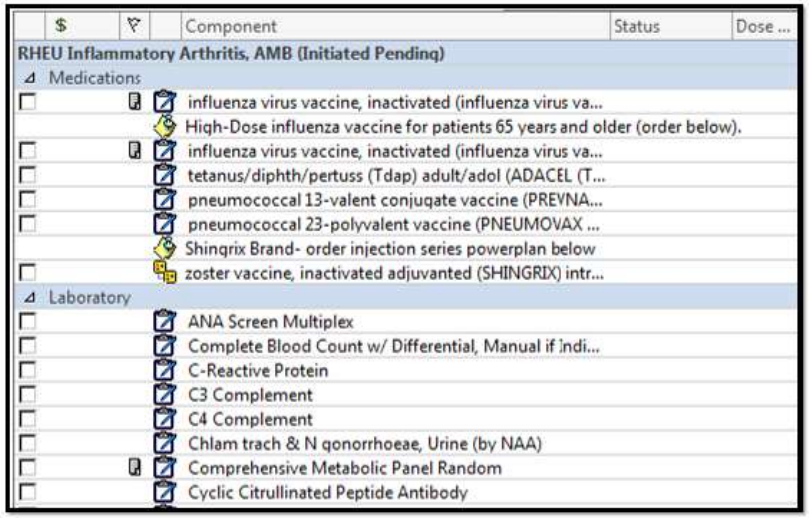
Rheumatoid arthritis is an incredibly heterogenous disease that differs substantially from patient to patient in both presentation and disease progression.

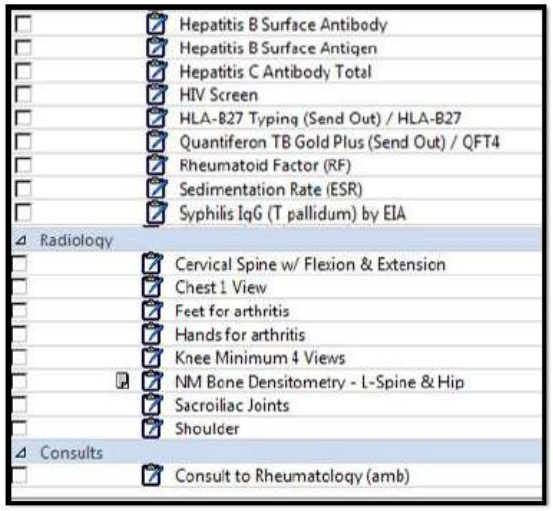
While rheumatoid arthritis is a common disease (affecting >1% of the adult population in the US or over 1.5 million people), many primary care providers see only a handful of patients and may not be comfortable with making the diagnosis or referring to a rheumatologist.

Inflammatory Arthritis Order Set

At Virginia Mason, our rheumatology group has created an order set to aid in appropriate initial testing for patients suspected of having inflammatory arthritis.

This order set can be found in Cerner under "RHEU Inflammatory Arthritis, AMB." This order set includes orders for initial lab work needed for diagnosis, screening lab work needed prior to initiation of DMARDs, orders for imaging of involved joints, and required vaccinations for patients on immunosuppressive treatment.





Thank you!

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Extra Slides

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ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Oliver Distler, M.D., Kristin B. Highland, M.D., Martina Gahlemann, M.D., Arata Azuma, M.D., Aryeh Fischer, M.D., Maureen D. Mayes, M.D., Ganesh Raghu, M.D., Wiebke Sauter, Ph.D., Mannaig Girard, M.Sc., Margarida Alves, M.D., Emmanuelle Clerisme-Beaty, M.D., Susanne Stowasser, M.D., et al., for the SENSCIS Trial Investigators*

June 27, 2019
N Engl J Med 2019; 380:2518-2528
DOI: 10.1056/NEJMoa1903076

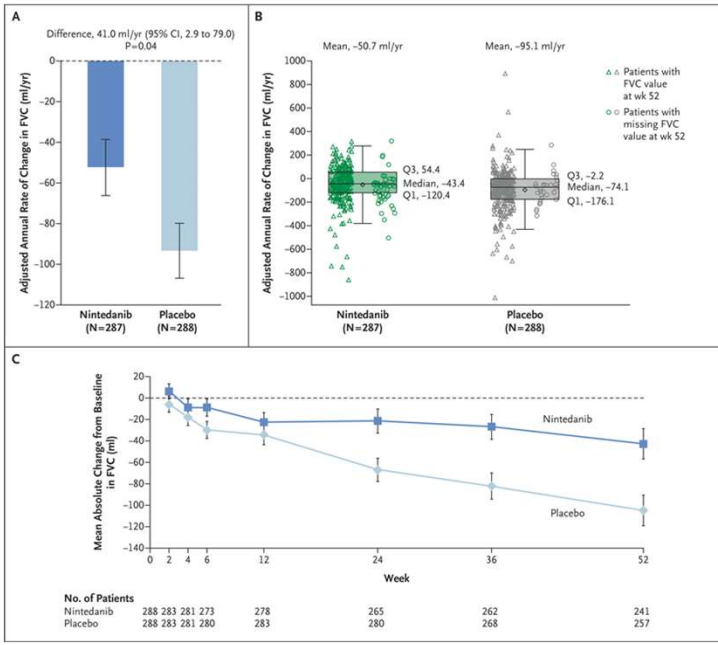
Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis and a leading cause of systemic sclerosis-related death.

Nintedanib, a tyrosine kinase inhibitor, has been shown to have antifibrotic and antiinflammatory effects in preclinical models of systemic sclerosis and ILD.

On the basis of evidence from two randomized, double-blind trials (Scleroderma Lung Studies I and II [SLS-I and SLS-II]), the immunosuppressants mycophenolate and cyclophosphamide are frequently used for the treatment of ILD associated with systemic sclerosis. In addition, targeted treatments are licensed to address other organ manifestations such as pulmonary arterial hypertension and digital ulcers.

Among patients with ILD associated with systemic sclerosis, the annual rate of decline in FVC was lower with nintedanib than with placebo; no clinical benefit of nintedanib was observed for other manifestations of systemic sclerosis.

The adverse-event profile of nintedanib observed in this trial was similar to that observed in patients with idiopathic pulmonary fibrosis; gastrointestinal adverse events, including diarrhea, were more common with nintedanib than with placebo



Background

- Nintedanib, an intracellular inhibitor of tyrosine kinases, is an approved treatment for idiopathic pulmonary fibrosis.

- In patients with IPF, treatment with nintedanib (150 mg twice daily) slowed disease progression by reducing the rate of decline of the forced vital capacity (FVC).

- Although idiopathic pulmonary fibrosis and ILD associated with systemic sclerosis have different triggers, the pathophysiological processes of both diseases include the transformation of fibroblasts to a myofibroblastic phenotype and the excess deposition of extracellular matrix.

- Nintedanib has shown antifibrotic, antiinflammatory, and vascular remodeling effects in several animal models resembling aspects of systemic sclerosis, ILD associated with systemic sclerosis, and other fibrosing ILDs, findings that suggest that nintedanib could modulate processes fundamental to the progression of fibrosis in humans.

- We conducted the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial to investigate the efficacy and safety of nintedanib in patients with ILD associated with systemic sclerosis.

Methods

- Randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of nintedanib in patients with ILD associated with systemic sclerosis

- Recruitment in 32 countries from November 2015 to October 2017

- Inclusion criteria: Patients 18 years or older who had systemic sclerosis per EULAR and ACR criteria with
  - An onset of the first non-Raynaud's symptom within the past 7 years and
  - A high-resolution computed tomographic scan that showed fibrosis affecting at least 10% of the lungs
  - Patients were required to have an FVC that was at least 40% of the predicted value and a diffusion capacity of the lung for carbon monoxide (DL_{CO}) (corrected for hemoglobin) that was 30 to 89% of the predicted value.
  - Patients who were receiving prednisone at a dose of up to 10 mg per day or mycophenolate or methotrexate at a stable dose for at least 6 months before randomization (or both therapies) could participate in the trial.
  - If clinically significant worsening of systemic sclerosis occurred during the trial, additional therapy was allowed

- Exclusion: Of the 819 patients screened, 4 who had clinically significant pulmonary hypertension (defined as previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterization with a cardiac index of ≤2 liters per minute per square meter of body-surface area, or pulmonary hypertension that led to parenteral therapy with epoprostenol or treprostinil) were excluded.

- Participants were randomly assigned, in a 1:1 ratio, to receive 150 mg of nintedanib, administered orally twice daily, or placebo

- Randomization was performed with the use of an interactive response system, and the patients were stratified according to the presence of antitopoisomerase I antibody, which has been associated with a decline in FVC in patients with early systemic sclerosis.[23] The primary efficacy evaluation was conducted at week 52. Patients continued to receive the assigned intervention in a blinded manner until the last patient reached week 52 but for no longer than 100 weeks. Patients who discontinued the intervention were asked to attend all scheduled visits and undergo examinations as originally planned. Patients who had adverse events were permitted to interrupt the course of their assigned intervention (for ≤4 weeks if they had an adverse event that was considered to be related to the intervention by the investigator or for ≤8 weeks for adverse events that were not considered to be related to the intervention) or to reduce the dose to 100 mg twice daily.

- The primary end point: annual rate of decline in forced vital capacity (FVC), assessed over a 52-week period.

- Key secondary end points:
  - Absolute changes from baseline in the modified Rodnan skin score
  - Total score on the St. George's Respiratory Questionnaire (SGRQ) at week 52.

Results

- A total of 576 patients received at least one dose of nintedanib or placebo
- 51.9% had diffuse cutaneous systemic sclerosis
- 48.4% were receiving mycophenolate at baseline

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Nintedanib (N=288)	Placebo (N=288)
Female sex — no. (%)	221 (76.7)	212 (73.6)
Age — yr	54.6±11.8	53.4±12.6
Diffuse cutaneous systemic sclerosis — no. (%)	153 (53.1)	146 (50.7)
Years since the onset of the first non-Raynaud's symptom		
Median	3.4	3.5
Range	0.3–7.1	0.4–7.2
Extent of fibrosis of the lungs on high-resolution CT — %	36.8±21.8	35.2±20.7
FVC — ml	2459±736	2541±816
FVC — % of predicted value	72.4±16.8	72.7±16.6
DL_{CO} — % of predicted value†	52.9±15.1	53.2±15.1
Antitopoisomerase antibody positive — no. (%)‡	173 (60.1)	177 (61.5)
Modified Rodnan skin score§	11.3±9.2	10.9±8.8
Patients with diffuse cutaneous systemic sclerosis	17.0±8.7	16.3±8.9
Patients with limited cutaneous systemic sclerosis	4.9±4.2	5.4±4.1
Total score on the SGRQ¶	40.7±20.2	39.4±20.9
Score on the HAQ-DI‖	0.65±0.70	0.55±0.58
Scaled score on the FACIT-Dyspnea questionnaire**	47.01±9.64	45.67±9.90
Receiving mycophenolate — no. (%)	139 (48.3)	140 (48.6)
Receiving methotrexate — no. (%)	23 (8.0)	15 (5.2)

* Plus–minus values are means ±SD. Data on some variables were not available for all patients. A larger table of baseline characteristics is included in section G in the Supplementary Appendix. CT denotes computed tomography, DL_{CO} diffusion capacity of the lungs for carbon monoxide, FACIT Functional Assessment of Chronic Illness Therapy, FVC forced vital capacity, HAQ-DI Health Assessment Questionnaire–Disability Index, and SGRQ St. George's Respiratory Questionnaire.

† The DL_{CO} value was corrected for the hemoglobin level. DL_{CO} values were available for 285 patients in the nintedanib group and 284 patients in the placebo group.

‡ Historical information on antitopoisomerase antibody status was used, or, if this information was not available to the trial sites, it was provided by a central laboratory.

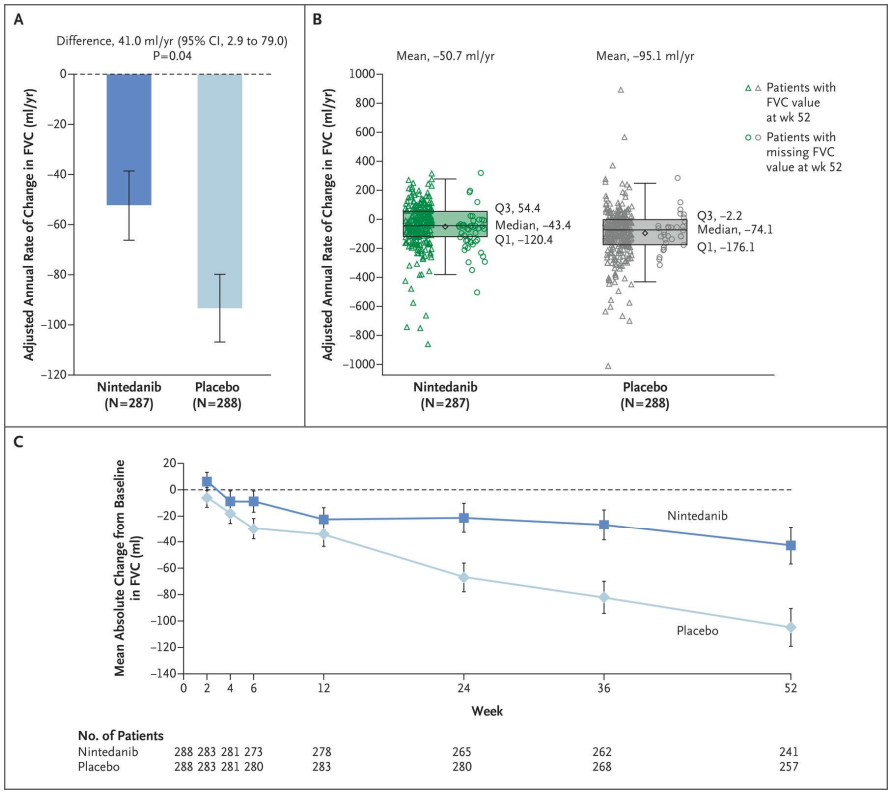
§ The modified Rodnan skin score is used to evaluate a patient's skin thickness through palpation of 17 areas; scores range from 0 to 3 for each area (to give a maximum score of 51), with higher scores indicating worse skin fibrosis. Scores were available for 288 patients in the nintedanib group and 286 patients in the placebo group. Among the patients with diffuse cutaneous systemic sclerosis, scores were available for 153 of those in the nintedanib group and for 144 of those in the placebo group. Among the patients with limited cutaneous systemic sclerosis, scores were available for 135 of those in nintedanib group and for 142 of those in placebo group.

¶ Total scores on the SGRQ range from 0 to 100, with higher scores indicating worse health-related quality of life. Scores were available for 282 patients in the nintedanib group and 283 patients in the placebo group.

‖ Scores on the HAQ-DI range from 0 to 3, with higher scores indicating worse disability. Scores were available for 283 patients in the nintedanib group and 281 patients in the placebo group.

** Scaled scores on the FACIT-Dyspnea questionnaire range from 27.7 to 75.9, with higher scores indicating worse dyspnea. Scores were available for 283 patients in the nintedanib group and 285 patients in the placebo group.

Results



In the primary end-point analysis, the adjusted annual rate of change in FVC was -52.4 ml per year in the nintedanib group and -93.3 ml per year in the placebo group (difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P = 0.04).

Sensitivity analyses based on multiple imputation for missing data yielded P values for the primary end point ranging from 0.06 to 0.10.

The change from baseline in the modified Rodnan skin score and the total score on the SGRQ at week 52 did not differ significantly between the trial groups, with differences of -0.21 (95% CI, -0.94 to 0.53; P = 0.58) and 1.69 (95% CI, -0.73 to 4.12 [not adjusted for multiple comparisons]), respectively.

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Nintedanib	Placebo	Difference (95% CI)
Primary end point			
Annual rate of decline in FVC assessed over 52 weeks — ml/yr	−52.4±13.8	−93.3±13.5	41.0 (2.9 to 79.0)†
Key secondary end points			
Absolute change from baseline in modified Rodnan skin score at week 52	−2.17±0.27	−1.96±0.26	−0.21 (−0.94 to 0.53)‡
Absolute change from baseline in total score on the SGRQ at week 52	0.81±0.88	−0.88±0.87	1.69 (−0.73 to 4.12)§
Other secondary end points			
Absolute change from baseline in FVC at week 52 — ml	−54.6±13.9	−101.0±13.6	46.4 (8.1 to 84.7)§
Annual rate of decline in FVC — % of predicted value	−1.4±0.4	−2.6±0.4	1.2 (0.1 to 2.2)§
Absolute change from baseline in DL_{CO} at week 52 — % of predicted value	−3.21±0.54	−2.77±0.54	−0.44 (−1.94 to 1.06)§
Absolute change from baseline in net digital ulcer burden at week 52	0.03±0.05	0.06±0.04	−0.03 (−0.16 to 0.09)§
Patients with an absolute decline from baseline in FVC of >5 percentage points of the predicted value at week 52 — no./total no. (%)	59/287 (20.6)	82/288 (28.5)	0.65 (0.44 to 0.96)§¶
Patients with an absolute decline from baseline in FVC of >10 percentage points of the predicted value at week 52 — no./total no. (%)	20/287 (7.0)	24/288 (8.3)	0.82 (0.44 to 1.52)§¶
Patients with a relative decline from baseline in FVC, measured in milliliters, of >5% at week 52 — no./total no. (%)	95/287 (33.1)	125/288 (43.4)	0.65 (0.46 to 0.91)§¶
Patients with a relative decline from baseline in FVC, measured in milliliters, of >10% at week 52 — no./total no. (%)	48/287 (16.7)	52/288 (18.1)	0.91 (0.59 to 1.41)§¶

* Changes from baseline are adjusted means ±SE based on the statistical models. Data on some variables were not available for all patients. FVC end points were analyzed in 287 patients in the nintedanib group and 288 patients in the placebo group, except for the absolute change from baseline in FVC in milliliters, which was analyzed in 288 patients in both groups. Modified Rodnan skin score was analyzed in 288 patients in the nintedanib group and 286 patients in the placebo group, total score on the SGRQ in 282 and 283 patients, DL_{CO} in 285 and 284 patients, and net digital ulcer burden (the number of fingers with ulcers of vascular origin distal to the proximal interphalangeal joints) in 288 patients in both groups.

† P=0.04.

‡ P=0.58.

§ The 95% confidence interval was not adjusted for multiple comparisons.

¶ The difference was assessed as an odds ratio.

Table 3. Adverse Events.*

Event	Nintedanib (N=288)	Placebo (N=288)
	no. of patients (%)	
Any adverse event	283 (98.3)	276 (95.8)
Most common adverse events†		
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Skin ulcer	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decrease	34 (11.8)	12 (4.2)
Severe adverse event‡	52 (18.1)	36 (12.5)
Serious adverse event§	69 (24.0)	62 (21.5)
Fatal adverse event	5 (1.7)	4 (1.4)
Adverse event leading to discontinuation of the intervention	46 (16.0)	25 (8.7)

* Adverse events, as reported over 52 weeks plus a 28-day post-treatment period, were coded according to the preferred terms in the *Medical Dictionary of Regulatory Activities*. Data are shown for the patients who had at least one such adverse event.

† The most common adverse events were those that were reported in more than 10% of the patients in either trial group.

‡ A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities.

§ A serious adverse event was defined as an event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.

Diarrhea, the most common adverse event, was reported in 75.7% of the patients in the nintedanib group and in 31.6% of those in the placebo group.

Limitations

- “The absolute between-group difference in the annual rate of decline in FVC observed in our trial (41 ml in favor of the nintedanib group) was smaller than assumed in the sample-size calculation. We speculate that this was because approximately half of the trial population were receiving mycophenolate at baseline and approximately half had limited cutaneous systemic sclerosis. This resulted in a trial population in which the decline in FVC in the placebo group was lower than assumed on the basis of historical data. The decline in FVC in the placebo group, as well as the magnitude of the effect of nintedanib, differed depending on mycophenolate use. Despite the large variability associated with the adjusted annual rates of decline in FVC observed in the current trial and the limitations inherent in comparing groups of patients who had not undergone randomization according to mycophenolate use, these data suggest a potential benefit of mycophenolate on lung function.”

- “However, because we excluded patients with clinically significant pulmonary hypertension, our data cannot be applied to such patients. The lower rate of decline in FVC in the nintedanib group was not accompanied by a benefit with respect to health-related quality of life.”

Conclusions

- Among patients with ILD associated with systemic sclerosis, the annual rate of decline in FVC was lower with nintedanib than with placebo; no clinical benefit of nintedanib was observed for other manifestations of systemic sclerosis.

- The adverse-event profile of nintedanib observed in this trial was similar to that observed in patients with idiopathic pulmonary fibrosis; gastrointestinal adverse events, including diarrhea, were more common with nintedanib than with placebo