Best of Immunology and Biologics Educational Collaborative (IBEC) 2016: Focus on Advancements in Rheumatoid and Inflammatory Arthritis

Advances in Immunotherapy: Checkpoint Therapy—Good for Oncology and a New Field for Rheumatology

Small Molecules for Inflammatory Arthritis: Benefits and Risks

Focus on Early RA—A 2016 Interview

Use of Biosimilars in Rheumatoid Arthritis

Original Release Date: December 15, 2016
Expiration Date: December 15, 2017
Estimated Time to Complete Activity: 1.25 hours

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This activity is supported by educational grants from Bristol-Myers Squibb, Lilly, and Pfizer
Table of Contents

4  Introduction

5  Advances in Immunotherapy: Checkpoint Therapy—Good for Oncology and a New Field for Rheumatology

8  Small Molecules for Inflammatory Arthritis: Benefits and Risks

14  Focus on Early RA—A 2016 Interview

16  Use of Biosimilars in Rheumatoid Arthritis

19  Posttest and Evaluation Form

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Published by Global Academy for Medical Education, LLC and Frontline Medical Communications, LLC at Rockville, MD. Content created by Vindico Medical Education at 6900 Grove Road, Building 100, Thorofare, NJ 08086-9447. Printed in the USA.

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Rheumatoid arthritis (RA) is a progressive and painful systemic inflammatory disease that preferentially attacks the synovium of the joint, leading to joint destruction, debility, and deformity. Increased understanding of the underlying pathophysiology of RA has made a remarkable difference in its treatment and prognosis. Numerous therapeutic agents with diverse targets and mechanisms have been added to the RA armamentarium, allowing for intervention at various stages in the pathogenic process of the disease. Mechanisms of autoimmunity and inflammation will be compared to the emerging role of checkpoint therapy and small molecules in novel treatment approaches. By understanding the underlying immunologic mechanisms driving RA progression, clinicians involved in the management of patients with RA will be better equipped to evaluate the clinical and pharmacologic safety, as well as efficacy profiles of current and emerging therapies. This monograph will review checkpoint and small molecule therapy for RA, as well as early RA and use of biosimilars in clinical practice.

Target Audience
The intended audience for this activity is rheumatologists, rheumatology nurses, and other healthcare professionals involved in the treatment of patients with RA.

Learning Objectives
Upon successful completion of this educational activity, participants should be better able to:

- Explain the clinical and immunologic progression of RA from asymptomatic autoimmunity to pre-RA and RA and relate the role of anti-citrullinated protein antibodies (ACPA(s)) and gene interactions to this process.
- Assess the scientific basis for small molecule therapy of RA and allied conditions (kinase inhibitors, PPD inhibitors, and others) as well as compare and contrast data on efficacy and toxicity from these agents versus other immune-based therapies.
- Detail the challenges in interpreting safety data from studies of biologic and immune-based therapies derived from randomized trials, extension studies, and registries.
- Examine the bioengineering and regulatory basis of biosimilar drug development and critically appraise both the advantages and risks of their potential use in practice.

CME Questions?
Contact us at CME@VindicoCME.com
Introduction

Significant research advancements in recent years have allowed greatly expanded treatment options and improved outcomes for patients with chronic diseases, including cancer and rheumatic disorders. Immune checkpoint inhibitors are now available for treating several cancer types, and their use requires diligent attention to preventing, identifying, and properly managing adverse events, for which evidence-based guidance is necessary. Development of rheumatic complications is receiving increased attention; however, the evidence base is inadequate, and additional data are needed.

In addition to the progress with large, monoclonal antibody-based immunotherapies, much advancement has been made in the development of novel, small molecule disease-modifying antirheumatic drugs (DMARDs). In comparison with biologics, these small molecules are bioavailable after oral administration, providing an important advantage as research seeks to develop therapies that can fill the unmet needs and limitations of currently available agents for treating inflammatory autoimmune diseases.

Several plausible molecular pathways and molecules have been identified as targets for new DMARDs. The US Food and Drug Administration has approved 2 agents targeting different pathways in the last 5 years, and other agents are in late-stage development. The volume of ongoing research challenges clinicians to maintain a current understanding of the state of the art as data are reported on new compounds and updates on the efficacy and safety of existing agents emerge.

To facilitate acquiring an up-to-date overview of the current status of potential rheumatic complications on checkpoint inhibitor therapy, and of the latest data describing the benefits and risks of small molecules for treating inflammatory arthritis, Vindico Medical Education arranged for experts in the field to share their knowledge and experience in these dynamic areas. Salient information is summarized, and reinforced by discussion of a real-world case.

I thank the authors for sharing their expertise and for helping with the preparation of this monograph. Readers can expect to gain an appreciation of the increasing importance of interdisciplinary management of patients with cancer, and to enhance their understanding of the rationale for and outcomes achieved by small molecule therapies.

Leonard H. Calabrese, DO
Activity Chair
Advances in Immunotherapy: Checkpoint Therapy—Good for Oncology and a New Field for Rheumatology

Leonard H. Calabrese, DO

As the science of immunology developed, accompanied by increased understanding of cancer pathogenic mechanisms, research oncologists directed considerable research focus on harnessing the immune system to overcome neoplasia. After disappointing beginnings, immunotherapy has made promising advancements in recent years. Checkpoint therapy is emerging as the next horizon of cancer management; tempered by the limitations that can be imposed by immune-related adverse events (irAEs).

T Cell Activation

The model of T cell activation in infection is informative to understanding the process and how it relates to autoimmunity. The immune response is launched by exposure of naïve T cells to an infecting agent. Once activated, T cells undergo clonal expansion, followed by homeostatic contraction once the infection is resolved (Figure 1). A reservoir of memory cells is created that can be recruited at the next infection with that agent.

Two signals are required for T cell activation, provided through 1) the T-cell antigen receptor, and 2) co-stimulatory molecules (Figure 2). The naïve T cell encounters the antigen to which it will respond in the secondary lymphoid tissue, when presented with a foreign peptide bound to a major histocompatibility complex (MHC) molecule on the surface of an activated antigen-presenting cell (APC). The most important APCs are highly specialized mature dendritic cells that express co-stimulatory cell surface molecules (B7) in the presence of infection that bind to CD28 on naïve T cells. Ligation of CD28 by B7 is the second required signal for T cell activation. The T cells are induced to proliferate and differentiate into progeny called effector T cells, by the autocrine action of the cytokine interleukin-2 (IL-2).

Effector T cells comprise several functional classes. The CD8 T cells differentiate into cytotoxic T cells, while CD4 T cells are a heterogeneous group currently comprising 5 classes (TH1, TH2, TH17, T follicular helper cells, regulatory T cells) distinguished by the cytokines that induce their differentiation, transcription factors that determine their differentiation, cytokines they secrete, and the cell types they affect.
When an antigenic signal is not accompanied by the requisite CD28-mediated co-stimulatory signal, the naïve T cell enters a state of irreversible anergy. Activated effector T cells do not require co-stimulation. Although most activated T cells become short-lived effector cells that die by apoptosis, some become long-lived memory cells.

**Checkpoint 1: CTLA-4**

CD28-related proteins induced on activated T cells include CTLA-4, which is also a B7 receptor, with an affinity for B7 that is approximately 20-fold greater than that of CD28. When CTLA-4 is preferentially bound to a B7 family molecule (CD80 or CD86), inhibitory signals limit the proliferative response of activated T cells as a natural check against overexuberant and perhaps dangerous responses, as well as autoimmunity and lymphoproliferative disease development. The importance of limiting T cell proliferative response was supported by fatal massive lymphocyte proliferation observed in mice genetically engineered to have a disrupted CTLA-4 gene.1

This phenomenon comprises checkpoint 1, with activities occurring in the T cell zone of the secondary lymphoid tissue. The therapeutic potential of this checkpoint was exploited with the development of the first antibody approved for use in cancer. Ipilimumab is a monoclonal antibody against cell surface CTLA-4, which was approved in North America and Europe for treating advanced cases of melanoma in 2011.2,3 Interrupting this checkpoint removes the negative inhibition of T-cell co-stimulation, maintaining T-cell effector function.

In rheumatology applications, abatacept is a soluble fusion protein that consists of the extracellular domain of CTLA-4 linked to the modified Fc portion of human IgG1.4 By binding to B7 on APC, abatacept blocks T cell CD28 from binding with its ligand, effectively inhibiting the essential co-stimulatory signal of T cell activation. Other indications for agents with this mechanism of action include graft rejection prophylaxis.2

**Checkpoint 2: PD-1**

The activated T cells are directed to the targeted peripheral tissue to initiate the effector phase of the immune response, where the second checkpoint is evidenced. In response to a virus infection, for example, each activated T cell may produce up to 50,000 cytotoxic T cells.2 After clearing the virus, approximately 95% of the CD8 T cell population undergoes apoptosis. The remaining cells that express the IL-7 receptor become long-lived, virus-specific memory cells.

Some pathogens, such as HIV, make rapid mutation and recombination changes to the surface antigens that allow them to escape targeted immune response.2 In the setting of antigen persistence, T cell effector functions are progressively lost, and the T cells enter a state of exhaustion.5 Although some residual function is retained, exhaustion is also accompanied by co-expression of high levels of inhibitory receptors, including programmed cell death-1 (PD-1), which can occur regardless of continuing T cell receptor stimulation. PD-1 is also expressed on other lymphocyte subsets, including B cells and natural killer (NK) cells.6 PD-1 must be engaged by one of its B7 family ligands, PD-1 ligand 1 (PD-L1) or 2 (PD-L2), to inhibit lymphocyte function.

Exhausted CD8 T cells initially lose cytolytic activity, IL-2 production, and proliferative capacity, followed by impaired production of other cytokines. Finally, exhausted T cells can be physically deleted.6 CD4 T cells also lose effector functions during chronic viral infections, with poor cytokine production and high PD-1 expression, and these losses may occur earlier than they do for CD8 T cells.7 Exhausted T memory cells that normally undergo antigen-independent proliferation induced by IL-7 and IL-15 become less responsive to these cytokines. Exhaustion is dissimilar to anergy, where cells enter a state of terminal hyporesponsiveness and fail to acquire effector functions as a result of antigen signaling without co-stimulation.8 Modulating checkpoint 2, using PD-1 pathway blockade, can partially reverse exhaustion and improve the immune response.

**Clinical Experience with Checkpoint Blockade Inhibition in Cancer**

Four monoclonal antibodies have received a US Food and Drug Administration (FDA) approval since 2011 for treating many cancer types using checkpoint blockade. One CTLA-4 antibody, 2 PD-1 antibodies, and a PD-L1 antibody are now available. Research continues, with studies of PD-1 and PD-L1 antibodies in at least 15 cancer types underway in 2015.8

**Anti-CTLA-4: Ipilimumab**

Ipilimumab was approved by the FDA in 2011 for treating advanced melanoma.9 In addition to favorable survival data from the Phase 3 pivotal trials, long-term data were reported from pooled Phase 2 and 3 trial data with up to 10 years follow-up, which revealed the survival curve began to plateau after about 3 years.9

**Anti-PD-1: Pembrolizumab and Nivolumab**

Pembrolizumab is FDA-approved with an indication for treating patients with unresectable or metastatic melanoma, metastatic non-small cell lung cancer (NSCLC) with PD-L1 expressing tumors, and with recurrent or metastatic head and neck squamous cell carcinoma.10 In 2015, pembrolizumab received FDA breakthrough therapy designation for treating patients with microsatellite instability high metastatic colorectal cancer.11

Nivolumab is FDA-approved for treating several cancers, with required disease characteristics and prior treatment status.12 Current indications include advanced melanoma, metastatic NSCLC, advanced renal cell carcinoma, and classical Hodgkin lymphoma.

In 2015, the FDA-approved nivolumab in combination with ipilimumab for treating patients with unresectable or metastatic melanoma.12,13 This marked the first FDA approval of an immunotherapy combination for treating cancer.

**Anti-PD-L1: Atezolizumab**

In 2016, atezolizumab was FDA-approved for treating patients with locally advanced or metastatic urothelial carcinoma, who have disease progression after previous specific therapies.14

**Immune-related Adverse Events**

The function of auto-reactive T cells is accomplished through the CTLA-4 and PD-1 axes.8 Accordingly, it is not surprising that irAEs observed with immune checkpoint blockade are similar to some of the clinical features of autoimmune diseases, which occur when T cells respond to self-antigens.

The irAE data are not uniformly collected, and grading systems are suboptimal, complicating acquiring reliable data on their incidence and severity. In general, irAEs occur more frequently in patients treated with anti-CTLA4 (~90%) compared with anti-PD-1/PDL-1 (~70%).8

During clinical trials of checkpoint inhibitors, irAEs were reported in all body systems, including musculoskeletal and rheumatic disease that are described in more detail below. Grade I-II irAEs were mainly observed in the skin after treatment with anti-CTLA-4 (30% to 40%) and anti-PD-1 (20% to 30%), followed by gastrointestinal (GI) tract (20% to 30% and 10% to 20%).9 The irAEs occurred among each system in <10% of patients in anti-PD-L1 trials. Grade III-V irAEs were reported in <5% of all patients with the exception of GI irAEs in patients treated with anti-CTLA-4, which occurred in over 10% of patients in most trials. IrAEs usually are observed within 3 to 6 months of starting anti-CTLA-4 or anti-PD-1 therapy; however, some irAEs have been reported months after ipilimumab treatment was discontinued.8,15
The irAE dose-dependency was noted with the anti-CTLA-4 antibody ipilimumab. A recent systematic review and meta-analysis included 81 articles reporting data from 22 studies of anti-CTLA-4 antibodies that included observational through randomized controlled trial designs. Any grade irAEs occurred in 72% of patients, while the incidence of grade ≥3 irAEs was 24%. The incidence of all grade irAEs for patients taking ipilimumab 3 mg/kg was 61%, increasing to 79% for 10 mg/kg. In the Phase 1 pembrolizumab KEYNOTE-001 expansion study, after a median of 11 months of follow-up, irAEs were more frequent in patients with melanoma taking pembrolizumab 10 mg/kg every 2 weeks (23%) compared with every 3-week treatment with 10 mg/kg (4%) or 2 mg/kg (9%), the recommended dose for this indication. However, cumulative toxicities with prolonged exposure to anti-PD-1 were not observed. There is some suggestion that having an irAE may predict favorable response to certain tumors, although the association has not been clearly established.

The irAEs are more common with combination therapy. This is consistent with the mechanisms of action of the 2 checkpoint inhibitors, which inhibit different lymphocyte subsets at different sites. In the Phase 3 CheckMate067 trial of combined nivolumab+ipilimumab compared with each agent as monotherapy, during a median ~12 months of follow-up, irAEs occurred in 55%, 27%, and 16% of patients taking nivolumab+ipilimumab, ipilimumab, and nivolumab, respectively.

### Checkpoint Inhibitor Treatment in Patients with Autoimmune Disease

Approximately 3% to 6% of the general population has an autoimmune disease; however, this usually an exclusion criterion for clinical trial participation. Accordingly, there are few reports in the literature of checkpoint inhibitor treatment in this subpopulation of patients with cancer. A case series of patients treated with ipilimumab included 30 who had preexisting autoimmune disorders, of whom 6 had rheumatoid arthritis. Of these, 8 (27%) experienced exacerbations of their autoimmune condition that were managed with systemic corticosteroids. Fifteen patients (50%) had neither irAEs nor flares of their underlying disorder, and 6 (20%) experienced complete or partial response. From this series, ipilimumab appears to be safe and effective in this patient population; however, diligent clinical monitoring is recommended for these patients.

A single center reported 254 of 298 (85%) patients receiving the standard ipilimumab dose for advanced melanoma had irAEs of any grade, which led to treatment discontinuation in 56 (19%). Systemic corticosteroid therapy was necessary for 103 (35%) patients, and 29 (10%) also required anti-TNFα treatment.

### Rheumatic Complications in Patients With Cancer on Checkpoint Inhibitor Treatment

Rheumatic complications in patients with cancer treated with checkpoint inhibitors are among the most poorly defined, with an incidence estimated at approximately 3%. In an expansion cohort from a Phase 1 nivolumab trial, data were reported on 129 patients with heavily treated advanced NSCLC with a median follow-up of 39 months (range 32 to 66 months). Arthralgia was reported in 5 (3.9%) patients across the 1, 3, and 10 mg/kg doses, without a dose-response observed (3.0%, 5.4%, 3.4%, respectively). All were grade 2. Myalgia was noted in 4 patients in the 1 mg/kg dose group, of which 1 case was both grades 3 and 4. The only other myalgia case was grade 2 in a patient taking 3 mg/kg nivolumab.

A median of 11 months of follow-up data were reported for 135 patients in the KEYNOTE-001 expansion trial of the safety and tumor responses to pembrolizumab 10 mg/kg every 2 weeks, and 10 and 2 mg/kg every 3 weeks. A dose-response effect in arthralgia was noted (21.1%, 12.5%, 4.5%, respectively), and myalgia was more common at the high dose (21.1%, 5.4%, 4.5%, respectively). None of these irAEs were grade 3.

In CheckMate067, safety data were reported for 937 patients after a median of ~12 months of follow-up. Arthralgia was noted in 6.1%, 7.7%, and 10.5% of patients in the ipilimumab, nivolumab, and nivolumab+ipilimumab groups, respectively. All cases were grade 2, with the exception of a single patient in the nivolumab+ipilimumab group (0.3%), who experienced grade 3 or 4 arthralgia.

A recent case series reported 13 patients who developed rheumatologic irAEs on immune checkpoint inhibitors, including inflammatory arthritis, synovitis, inflammatory synovial fluid, and sicca syndrome with severe salivary hypofunction. Corticosteroid treatment was often needed. There were 6 patients with inflammatory arthritis that varied in pattern. One patient’s inflammatory arthritis persisted for 6 months after stopping nivolumab, and another had active inflammatory arthritis 15 months after stopping ipilimumab+nivolumab. Treatment was intensified with the addition of TNF-inhibitors, and the arthritis was controlled. The authors noted that rheumatologists should acquire baseline and follow-up data of patients taking immune checkpoint inhibitors to provide important information about the development and manifestations of inflammatory arthritis in these patients, and help contribute a denominator to acquire a more accurate rheumatic irAE incidence.

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**Table. Management of irAEs (Excluding Skin and Endocrine Toxicities)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Follow-up Monitoring</th>
</tr>
</thead>
</table>
| 1     | • Continue immunotherapy  
       | • Treat symptoms         | • Frequent monitoring  
       |                  | • Treat worsening AE as grade 2 or 3/4 |
| 2     | • Delay immunotherapy  
       | • Treat symptoms         | • Resume immunotherapy when symptoms improve to grade 1  
       |                  | • Consider glucocorticosteroids 0.5 to 1.0 mg/kg/day if symptoms persist >5 to 7 days  
       |                  | • If worsens on steroids: treat as grade 3/4 |
| 3/4   | • Discontinue immunotherapy  
       | • Initiate glucocorticosteroids  
       | • 1 to 2 mg/kg/day  
       | • Consider hospitalization | • Continue glucocorticosteroids until grade 1  
       |                  | • Taper steroid dose over ≥1 month  
       |                  | • If persistent or worsening: consider alternative immunosuppressive therapy |

Small Molecules for Inflammatory Arthritis: Benefits and Risks

Jonathan Kay, MD

The potential for oral small molecules to treat inflammatory diseases has been under investigation for years; however, exploring these potential therapeutic drugs has not yet acquired a major research presence. A review of the US National Institutes of Health (NIH) clinical trial registry revealed that only 9% of rheumatoid arthritis trials were conducted with small molecules.1

Three oral small molecule products currently have US Food and Drug Administration (FDA) approval. Cyclosporine has been used for several decades as at least second-line therapy in rheumatoid arthritis (RA) and psoriasis.2,3 Tofacitinib was FDA-approved in 2012 as second-line RA treatment, and apremilast in 2014 for treating psoriatic arthritis and plaque psoriasis.4,5 Phase 3 data for RA treatment with baricitinib have been submitted to the FDA for review,6 and several other agents are in Phase 3 clinical trial stages (Table 1)(Figure 1).7 Many more are in Phase 2 stage clinical trials, including 3 agents targeting Bruton’s tyrosine kinase (M2951, CC-292, ACP-196).

Apremilast: Phosphodiesterase 4 Inhibitor

Second messengers, such as cyclic AMP (cAMP), are responsible for regulating intracellular signaling and responses to environmental factors.8 Phosphodiesterase 4 (PDE4) catalyzes conversion of cAMP to AMP, decreasing intracellular cAMP, which results in increased production of pro-inflammatory mediators and decreased production of anti-inflammatory mediators. Conversely, increases in intracellular cAMP result in cAMP-dependent protein kinase A activation, which activates transcription factors that modulate the production of pro- and anti-inflammatory mediators.

Apremilast is a PDE4 inhibitor indicated for treating adults with active psoriatic arthritis and patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy.4 Preclinical studies revealed effects on several receptors and cytokines associated with the pathophysiology of psoriasis and arthritis, including decreases in the expression of inducible nitric oxide synthase, TNF-α, IFN-γ, and IL-23, with increases in IL-10.8 Therefore, apremilast PDE4 inhibition resulted in decreased production of pro-inflammatory mediators and increased production of anti-inflammatory mediators.

<table>
<thead>
<tr>
<th>Table 1. New Small Molecules for Inflammatory Arthritis: Development Status August 2016</th>
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<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Apremilast</td>
</tr>
<tr>
<td>Tofacitinib</td>
</tr>
<tr>
<td>Baricitinib</td>
</tr>
<tr>
<td>Peficitinib (ASP015K)</td>
</tr>
<tr>
<td>ABT-494</td>
</tr>
<tr>
<td>Filgotinib</td>
</tr>
<tr>
<td>CF-101</td>
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</tbody>
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A3AR=A3 adenosine receptor; JAK=Janus kinase; PDE-4=Phosphodiesterase-4
Source: ClinicalTrials.gov; Prescribing information for approved agents.
Psoriatic Arthritis
Sixteen-week data from 3 pivotal Phase 3 trials (PALACE 1, 2, 3) of 20 mg or 30 mg apremilast twice daily compared with placebo supported the FDA approval of the safety and efficacy of apremilast for treating psoriatic arthritis.4 PALACE 3 had the same inclusion criteria as PALACE 1 and 2 (duration ≥6 months, ≥3 swollen, and ≥3 tender joints despite past or current disease-modifying antirheumatic drugs [DMARDs] and/or biologics), with the additional requirement of at least 1 psoriatic lesion ≥2 cm. The primary outcome was the proportion of patients achieving 20% improvement in modified American College of Rheumatology response criteria (ACR20) at week 16. The 3 trials now have 52-week data that continue to support the clinical improvements achieved on apremilast.9 Week 52 data for PALACE 1 and 3 revealed ACR20 was achieved by 55% to 63% of patients in both apremilast dose groups.10,11

Diarrhea, nausea, headache, and upper respiratory tract infection were the most common adverse events, and most were mild-to-moderate in severity. Diarrhea and nausea usually occurred early and were self-limited. Laboratory abnormalities were infrequent and transient. PALACE 4 compared 20 and 30 mg twice daily apremilast with placebo in patients who were DMARD-naïve.12 At week 16, ACR20 was achieved in significantly more apremilast patients in both groups compared with placebo (28% and 31% vs 16%, respectively; P≤0.01), with 53% and 59% achieving ACR20 at week 52.

Severe Plaque Psoriasis
A Phase 2b dose-ranging study evaluated 3 apremilast dose groups compared with placebo in 352 patients with moderate-to-severe plaque psoriasis.13 The primary endpoint, the proportion of patients achieving ≥75% reduction from baseline psoriasis area and severity index (PASI-75) at week 16, was achieved by 6%, 11%, 29%, and 41% of patients in the placebo, 10 mg, 20 mg, and 30 mg twice daily groups, respectively, (P<0.001 for 20 and 30 mg vs placebo). Apremilast was well tolerated. Most adverse events (AEs) were mild or moderate, and consistent with PDE inhibition (headache, diarrhea, nausea, vomiting). No serious AEs (SAEs) were judged to be treatment-related.

ESTEEM 1 and 2 provided the pivotal Phase 3 data for FDA approval of apremilast 30 mg twice daily for treating severe plaque psoriasis.4 The primary endpoint was the proportion achieving a ≥75% reduction from baseline Psoriasis Area and Severity Index (PASI-75) score at week 16. The placebo group switched to apremilast through week 32, followed by a randomized withdrawal phase to week 52. PASI-75 was achieved by significantly more apremilast compared with placebo group patients in both ESTEEM 1 (33% vs 5%; P<0.001) and ESTEEM 2 (29% vs 6%; P<0.001).14,15 Responses were maintained through 52 weeks in both studies. The AEs were mainly mild-to-moderate, and comparable among groups, with 56% and 69% of placebo and apremilast patients having one or more AEs during the placebo-controlled period. At that reporting, apremilast had been studied in >4,000 patients, and the safety profile was consistent across indications.

Tofacitinib: Janus Kinase Inhibitor

JAK-STAT Signaling
Approximately 60 cytokines that are important in the immune response bind to Type I/II receptors.5,16-20 All Type I/II receptors selectively associate with 1 of the Janus kinase (JAK: JAK1-3 and TYK2) family of tyrosine kinases, which is necessary for intracellular signaling and cell reactivity. The JAK signaling pathway is launched with the interaction of specific JAKs with transmembrane cytokine activated receptors JAK, inducing dimerization and activation. The selective receptor association defines their distinct roles. JAK3 associates with only 1 cytokine receptor, the common γ chain, which is that used by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. In the next step, the JAKs phosphorylate each other, the intracellular tail of the receptor, and signal transducers and activators of transcription (STATs). Seven STATs have been identified, and different cytokines have a propensity to activate specific STATs. The activated STATs also dimerize, and enter the nucleus where they affect gene expression. This simple pathway allows efficient communication between cytokine receptors and the cell nucleus.

When mutations in genes encoding specific JAKs and STATs were shown to be associated with human diseases, the possibility of therapeutic interventions emerged. Expanding understanding of this pathway, its components, and consequences of disruption led to the exploration of targeting JAKs as a potentially new class of immunomodulatory drugs.

Tofacitinib Development
Tofacitinib is a JAK inhibitor that has greater selectivity for JAK3 in vitro, with ~30- and 100-fold less potency for JAK2 and JAK1, and little effect on TYK2.16,21 In preclinical studies, tofacitinib was more effective than cyclosporine A in preventing transplant rejection in a nonhuman primate renal transplant model. Tofacitinib treatment was associated with a dose-dependent reduction of circulating CD16/56+ NKC, which reached an estimated maximum after approximately 8 to 10 weeks, and resolved within 2 to 6 weeks after discontinuing treatment.5 Treatment was also associated with dose-dependent increases in B cells, with small and inconsistent changes in T cells. Serum C-reactive protein decreases rapidly after starting treatment, and remains low throughout treatment.

Tofacitinib is indicated for the treatment of adult patients with moderate-to-severe active RA who have had an inadequate response or intolerance to methotrexate (MTX).5 Tofacitinib can be given as a monotherapy or in combination with MTX or other nonbiologic DMARDs. The recommended dose is 5 mg twice daily, or 11 mg of the extended-release formulation once daily.

Figure 2. ACR20 Outcomes in Pivotal Phase 3 Tofacitinib Trials

*P<0.05, **P<0.001, ***P<0.0001 vs. placebo or MTX (Start).
Follow-up: 3 months for Step/Solo; 6 months for others
BID=twice daily, DMARD= disease-modifying antirheumatic drug, IR=inadequate response, MTX=methotrexate, TNFi=tumor necrosis factor inhibitor
Tofacitinib Pivotal Trials

Data supporting the FDA approval of tofacitinib were provided by 2 dose-ranging and 5 6-month to 2-year confirmatory trials: ORAL Sync,22 ORAL Standard,23 ORAL Solo,24 ORAL Scan,25 ORAL Step,26 and ORAL Start.27 Five trials enrolled patients who had inadequate response to other treatments, and ORAL Start enrolled MTX-naïve patients. Both 5- and 6-mg tofacitinib twice-daily dose groups had superior ACR20 responses (Figure 2) that were consistent at 6 and 12 months in the 12-month trials.5

The long-term safety of tofacitinib was assessed from pooled extension study data that included patients in qualifying Phase 1, 2, and 3 studies.28 The 4102 patients were treated for 5963 patient-years, with a mean 531-day treatment beyond the original exposure in the index trial and a maximum of 1844 days. Nasopharyngitis (12.7%) and upper respiratory tract infection (10.5%) were the most common AEs. The SAEs were reported in 15.4% of patients, at an estimated rate of 11.1 events/100 patient-years, and serious infections at 3.1 events/100 patient-years. Laboratory values were stable over time and consistent with those during the studies. Persistent efficacy was observed through 48 months. Safety and efficacy were similar in patients receiving tofacitinib as monotherapy or with background nonbiologic DMARDs.

A post hoc analysis of ORAL Start data explored efficacy and safety in subgroups of patients with early (disease duration <1 year) and established (≥1 year) RA.30 Efficacy outcomes were generally similar between the 2 groups in the 2-year study, and no meaningful differences in safety endpoints were observed.

The relationship between malignancies and RA is complex; however, a malignancy risk associated with RA and with treatments for chronic inflammation is acknowledged. Accordingly, close monitoring of safety events of special interest is essential for treatment with immunomodulatory agents with new mechanisms of action. Pooled tofacitinib trial data comprising 5671 tofacitinib-treated patients were assessed for malignancy development, which revealed that incidence rates and types of malignancies remained stable with increasing 6-month periods of tofacitinib exposure.30 The overall median exposure was 2.35 years; longer-term surveillance is necessary.

JAK Inhibitors in the Pipeline

Baricitinib: Rheumatoid Arthritis

The FDA is currently reviewing data from 4 pivotal Phase 3 trials of baricitinib, a JAK inhibitor with JAK1/JAK2 selectivity. RA-BEACON enrolled 527 patients with moderately-to-severely active RA who did not respond to or who had unacceptable adverse effects with biologic DMARDs, who were randomized to 2 doses of baricitinib and placebo, continuing the therapies they were on at enrollment.31 The primary endpoint was the proportion of patients with ACR20 at week 12, which was significantly greater for the 4 mg baricitinib once daily dose compared with placebo (55% vs 27%; P<0.001), and remained elevated after 24 weeks. There were more AEs, including infections, with baricitinib compared with placebo treatment; however, SAEs were comparable among groups. Abnormal laboratory test results included significant LDL-C and creatinine level increases from baseline. Longer studies are needed to further assess safety and response durability. A 4-year extension study, RA-BEYOND, is recruiting patients who completed a previous baricitinib RA study, with a targeted completion date of early 2021.32 Pooled clinical trial data are emerging, and are currently available from 3464 patients with >1 year baricitinib exposure in 2166 patients and >2 years in 467 patients that suggest that the risk of AEs of interest does not increase with longer exposure.33

RA-BEAM was a 52-week Phase 3 study that randomized 1305 patients with moderately or severely active RA despite stable background MTX to placebo, baricitinib 4 mg orally once daily, and adalimumab 40 mg subcutaneously biweekly.34,35 Nonresponders were rescued with baricitinib starting at week 16, and all placebo group patients were switched to baricitinib from week 24 through week 52. Rescue rates were 26%, 7%, and 12%, respectively. Compared with placebo, significant improvements in ACR20 were observed in the baricitinib and adalimumab groups at weeks 12 (70% and 61% vs 40%; P<0.001) and 24 (74% and 66% vs 37%; P<0.001). Other outcomes, including ACR50/70, were also significantly better in the baricitinib compared with placebo group. Baricitinib was superior to adalimumab at weeks 24 and/or 12 for several outcomes, including ACR20/70 and improvement in DAS28-CRP. Treatment-emergent AEs (TEAEs) were higher for baricitinib and adalimumab compared with placebo; however, SAEs were lower in the baricitinib group and were similar to placebo in the adalimumab group.

The 24-week Phase 3 RA-BUILD enrolled 684 patients with active RA and IR or intolerance to ≥1 conventional DMARD, who were randomized into placebo, baricitinib 2 mg, and baricitinib 4 mg groups.36 As in other baricitinib studies, improvements in clinical measures were observed as early as week 1, and were more robust across all outcomes in the 4 mg group. Baricitinib had an acceptable safety and tolerability profile.

The noninferiority Phase 3 trial, RA-BEGIN, enrolled patients with limited or no treatment history with MTX and who were naïve to DMARDs, comparing baricitinib 4 mg as a monotherapy with baricitinib+MTX, and with MTX monotherapy as the active comparator.37 Rescue was not allowed prior to week 24, when all primary and major secondary endpoints were assessed. At week 24, ACR20 was superior in the baricitinib monotherapy and combination groups compared with the MTX group (77% and 78% vs 62%, respectively; P≤0.01), as were many secondary measures of disease activity. The TEAEs and SAEs were comparable among groups.

The ability to identify patients who are not likely to benefit from treatment could allow more efficient personalized medicine. Across RA-BUILD, RA-BEACON, RA-BEAM, and RA-BEGIN, a lack of early clinical response (failure to achieve a decrease in DAS28 ≥0.6 and/or CDAI 26 after 4 treatment weeks) was reported to be associated with very low rates of low disease activity or remission at 12 or 24 weeks.38,39

Peficitinib (ASP015K): Phase 2 Psoriasis

Peficitinib is an oral JAK inhibitor with moderate selectivity for JAK3 over JAK1/2, which is under development as a potential monotherapy in moderate-to-severe psoriasis. A Phase 2a study enrolled 5 sequential cohorts of 4 twice-daily dosing groups (10, 25, 60, 100 mg) and a once-daily dosing group (50 mg) for 6 weeks (n=124). The primary endpoint of mean change in PASI score from baseline was -7 for combined peficitinib groups (n=95), compared with -4 for the placebo group (P<0.001).40 Changes from baseline were significantly different in all pairwise comparisons of peficitinib dose groups and the placebo group. Similar improvements in efficacy endpoints were observed in the 10 and 25 mg twice-daily groups. PASI score changes from baseline ranged from -6 to 10 mg twice daily to -12 for 100 mg twice daily. The PASI scores decreased -7 points for the 25 mg twice daily and the 50 mg once daily groups.

Peficitinib was well tolerated at all doses. AEs occurred in 38% of 29 placebo patients and in 32% (50 mg once daily) to 65% (100 mg twice daily) of peficitinib patients. In the entire peficitinib cohort, 46% of patients experienced an AE. All AEs were mild or moderate in severity, and there were no SAEs.
**Peficitinib: Phase 2 Rheumatoid Arthritis**

A dose-ranging Phase 2b study was performed in 289 DMARD-inadequate responders (DMARD-IR) comparing 25, 50, 100, and 150 mg peficitinib once daily with placebo. The 2 highest doses had significantly more ACR20 responders at 12 weeks compared with placebo. The AEs were comparable in combined treatment and placebo groups, including SAEs and infections.

Another Phase 2b study enrolled 378 patients with MTX-IR RA, comparing the 4 doses of peficitinib (25 to 150 mg daily) to placebo+MTX. A dose-response effect was not observed, with ACR20 achieved by more patients taking 50 (P<0.05) and 150 mg (NS) peficitinib. Outcomes varied by geographic areas; European centers exclusively had significant improvement in ACR20 in both the 100 and 150 mg groups. The AEs were comparable among groups; however, more AEs leading to study discontinuation and the 3 SAEs occurred in the 100 and 500 mg groups.

A 4-group Phase 3 trial is underway in patients with DMARD-IR RA comparing 2 doses of peficitinib with placebo and etanercept. An enrollment of 500 is targeted, with completion estimated in early 2017. Another Phase 3 study is recruiting MTX-IR patients to compare 2 doses of peficitinib with placebo+MTX, expecting an enrollment of 510 and completion in early 2017. An extension study is enrolling patients who completed Phase 2b or Phase 3 studies, which estimates an enrollment of 800 and completion in late 2018.

**Filgotinib**

Filgotinib, which targets JAK1 with approximately 30-fold greater selectivity compared with JAK2 in whole blood assays, had comparable efficacy to etanercept in an arthritis model. Development has progressed through Phase 3 studies in RA. The Phase 2b dose-ranging DARWIN 1 study enrolled 594 patients with active RA on background therapy with a stable dose of MTX, who were randomized to placebo or 1 of 6 filgotinib groups. Daily doses of 50, 100, and 200 mg filgotinib were provided using a once-daily or twice-daily regimen for 24 weeks. The primary endpoint was ACR20 at week 12, with the 200 mg once daily and 100 mg twice daily groups having significantly greater responses compared with placebo (60% and 80% vs 45%, respectively; P=0.05 and P<0.001). All filgotinib doses had superior ACR50 compared with placebo (32% to 55% vs 15%, respectively; P<0.05 for all), and ACR70 was also superior in the 200 mg/day groups (24% and 31% vs 8%, respectively; P<0.05 and P<0.01). Filgotinib had a favorable safety profile, consistent with previous filgotinib studies in patients with RA.

DARWIN 2 randomized 287 patients with active RA with an inadequate response to MTX to placebo or filgotinib 50, 100, or 200 mg as a once daily regimen for 24 weeks. A 24-week MTX washout preceded enrolment. The 12-week ACR20 was significantly greater in the 3 filgotinib groups compared with placebo (67%, 66%, and 73% vs 31%, respectively; P<0.001 for all comparisons). ACR50 was also significantly greater in all 3 groups compared with placebo (34% to 44% vs 11%, respectively; P<0.01). The SAEs and TEAEs were comparable among groups. At 24 weeks, filgotinib groups had small increases in hemoglobin, creatinine, and lipids; a decrease in neutrophils; and minimal impact on LFTs.

DARWIN3 is a long-term open-label extension study available for patients who completed DARWIN 1 or DARWIN 2. The filgotinib 200 mg daily dose will be taken as a single 200 mg capsule or as 100 mg capsules twice daily for approximately 5 years. Enrollment is targeted at 600 participants, with estimated completion in early 2019.

Two Phase 3 trials are underway. Two doses of filgotinib+MTX and a single filgotinib monotherapy dose will be explored using MTX as the active comparator in MTX-naïve patients with RA. Enrollment of 1200 patients is planned, with a completion date in late 2020. The second Phase 3 study is enrolling patients with RA with an inadequate response to biologic DMARDs. Two doses of filgotinib will be compared with placebo in patients with stable ongoing treatment with 1 or 2 conventional synthetic DMARDs. An enrollment of 423 is targeted, with estimated completion in late 2018.

**ABT-494**

ABT-494 is a JAK inhibitor with enhanced selectivity for JAK1 over other JAK isoforms. The Phase 2b BALANCE I study evaluated twice daily 3, 6, 12, or 18 mg ABT-494 in 276 patients with moderate-to-severe RA who had an inadequate response or intolerance to ≥1 anti-TNF therapy. Significantly more patients in the ABT-494 groups achieved ACR20 compared with placebo group patients (53% to 71% vs 34%, respectively; P<0.05). Other efficacy outcomes were also superior with ABT-494. Significant differences were observed at week 2 for the 6 to 18 mg doses. Infection rates were higher in the 12 and 18 mg ABT-494 groups (40% and 38%) compared with placebo (23%) and 3 and 6 mg ABT-494 groups (20% and 22%), but none were serious.

The Phase 2b BALANCE II study evaluated 3, 6, 12, and 18 mg twice-daily and 24 mg once daily compared with placebo in 300 patients with MTX-IR RA. At 12 weeks, all doses had greater ACR20 responses compared with placebo, with significant differences compared with placebo at week 2. The AEs were similar among groups, and similar to those of other JAK inhibitors.

Five large Phase 3 trials are underway to further assess the safety and efficacy of ABT-494 in different RA patient populations: Select Compare, Select Next, Select Monotherapy, Select Beyond, and Select Early. Targeted enrollment for these trials is more than 4000 patients, with estimated completion of the 5 trials by 2021.

**Decernotinib (VX-509)**

Decernotinib is a JAK3 inhibitor that has reached Phase 2 in RA clinical trials. Preclinical data showed selectivity over the other JAK enzymes of 25- to 150-fold in cellular assays. Superior efficacy to etanercept was shown in a rat RA model.

A Phase 2a study compared 4 decernotinib doses with placebo in 204 adults with active RA who had been unsuccessfully treated with ≥1 DMARD. Patients were given 25, 50, 100, or 150 mg twice daily, after a defined washout period for their current therapies. ACR20 response rates at week 12 were 39%, 61%, 65%, and 66%, respectively, which were significantly greater in the 3 higher doses compared with placebo (29%; P≤0.01). Increased infections and elevated liver function studies were noted in the decernotinib groups as possible safety signals. Another Phase 2b dose-ranging study included 358 patients with RA with an inadequate response to MTX, who were randomized to placebo or 100, 150, or 200 mg decernotinib once daily, or 100 mg twice daily. All decernotinib dose groups had superior ACR20 (47%, 67%, 57%, 68% vs 18%, respectively; all P<0.001) and ACR50 (23%, 39%, 35%, 39% vs 7%, respectively; all P<0.01) responses compared with placebo at 12 weeks, which were maintained through week 24, at which time all doses were also statistically superior to placebo for ACR70. The safety profile was similar to that observed in the Phase 2a study. There were more infections in the decernotinib compared with control groups (29% vs 16%), with serious infections in 3.5% and 1.4% of decernotinib and placebo patients. Its status for continuing development is not clear at this time.
CF101: A3 Adenosine Receptor Agonist

Interest in the therapeutic potential of the A3 adenosine receptor (A3AR) was based on its overexpression in cancer and inflammatory cells, and in peripheral blood mononuclear cells of patients with cancer and inflammatory diseases.58 Synthetic, highly selective A3AR agonists, such as CF101, were shown to induce specific anti-inflammatory effects, with a protective effect on normal cells.

Rheumatoid Arthritis

A Phase 2 trial of CF101 included 74 patients with RA randomized to 0.1, 1.0, or 4.0 mg CF101 twice daily for 12 weeks.39 Although improvements in signs and symptoms were observed after 12 weeks, they did not reach statistical significance, and response was generally lowest in the 4.0 mg group. However, a significant correlation between A3AR overexpression at baseline and ACR50 and ACR70 responses was observed ($P=0.036$). Treatment was well tolerated, with mild headache (4.1%), nausea (2.7%), and rash (2.7%) the most common TEAEs. A subsequent Phase 2 study enrolled 79 patients with RA who had documented A3AR overexpression.60 The ACR20 was significantly higher in the CF101 compared with the placebo group at week 12 (49% vs 25%; $P=0.0352$), and response was highest in treatment-naïve patients.

A 4-group Phase 3 study is not yet open for enrollment, which will compare the 1 and 2 mg twice daily CT101 dose for 12 weeks with MTX and placebo in MTX-naive patients, without A3AR status enrollment limitations.61 The study will be performed at 2 centers in Israel, and expects to enroll 525 patients with an estimated completion date of late 2018.

Plaque Psoriasis

In a Phase 2 trial of CF101 in patients with severe plaque-type psoriasis, 75 patients were treated with 1, 2, or 4 mg CF101 twice daily for 12 weeks.62 The 2-mg group had statistically significant differences in PASI score compared with placebo at 8 ($P=0.047$) and 12 ($P=0.031$) weeks. Treatment was well tolerated. A Phase 2/3 study compared CF101 1 or 2 mg with placebo twice daily.63 At week 12 or 16 the placebo group crossed over to CF101 through week 32. The primary endpoint was proportion of patients achieving PASI-75. The study did not meet the week 12 primary efficacy endpoint, with PASI-75 achieved by 5.9% of 2 mg CF101 patients and 6.9% of placebo patients ($P=0.621$). However, PASI mean improvement at week 32 compared with baseline was 57% ($P<0.001$). The continued improvement over time warranted development of Phase 3 study protocols that have not yet been initiated.

Phase 3 Disappointments

In this dynamic environment, occasionally agents reach Phase 3 stages of development for a specific indication without going further. For example, masitinib (AB1010) is a tyrosine kinase inhibitor that targets the stem cell factor receptor KIT, which is a target for many inflammatory disease therapies.64 After an encouraging dose-ranging Phase 2a study in patients with active RA,65 the sponsor announced in 2015 that the ongoing Phase 3 trial was stopped for futility.66 Several masitinib Phase 3 trials for other indications including asthma, Alzheimer’s disease, multiple sclerosis, amyotrophic lateral sclerosis, and for various oncology and hematology indications are ongoing.67

Postmatinib is a small-molecule spleen tyrosine kinase (Syk) inhibitor, which progressed to a major Phase 3 clinical trial program.68 Disappointing efficacy in these trials led to a decision against pursuing regulatory approval for this indication.

Summary

Oral small molecules have been approved by the FDA for rheumatoid arthritis, psoriatic arthritis, and severe plaque psoriasis, and are in development for other inflammatory diseases. The PDE4 is the target of apremilast, which is approved for treating psoriatic arthritis and severe plaque psoriasis. The JAK3 inhibitor tofacitinib is FDA-approved for treating rheumatoid arthritis, and baricitinib, with JAK1/J2 selectivity, is under FDA review for the same indication. When combined with MTX, oral small molecules have efficacy and safety comparable to biologic agents.

References


Focus on Early RA—A 2016 Interview

William F.C. Rigby, MD

New EULAR Guidelines

Please discuss the current EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs.

The 2016 EULAR guideline1 update provides more awareness and clarity about the use of glucocorticoids, and the use of biological DMARDs (bDMARDs) in combination with methotrexate rather than as monotherapies. The guidelines now recommend that bDMARDs and targeted synthetic DMARDs (tsDMARDs) should be combined with a csDMARD. In patients who cannot use csDMARDs as a monotherapy, the guidelines recommend that IL-6 pathway inhibitors and tsDMARDs may have advantages compared with other bDMARDs.

A striking feature of these guidelines is they do not consider disease duration as a factor guiding treatment. Rather, the disease stages are addressed by treatment phases. There is conventional synthetic DMARD-(csDMARD) naive, commonly known as methotrexate-naive, csDMARD experienced but not responsive, and bDMARD experienced, meaning a bDMARD inadequate responder.

The EULAR guidelines suggest that treatment for patients with Phase 1 disease, that is, with a clinical diagnosis of RA who are csDMARD-naive, depends on the suitability of methotrexate. If methotrexate is not contraindicated, treatment with methotrexate combined with short-term glucocorticoids should be initiated. However, by stating that methotrexate should be part of the first treatment strategy, combination csDMARD treatment is not excluded; rather, it is not primarily recommended. This rewording was based on several recent trials showing that methotrexate monotherapy in combination with glucocorticoids is not less efficacious than combinations of csDMARDs plus glucocorticoids, but has less safety issues. For patients with a contraindication for methotrexate, leflunomide or sulfasalazine, with short-term glucocorticoid, is appropriate.

If the treatment target, low disease activity or remission within 6 months, is achieved, continue with this therapy. If Phase 1 treatment fails for lack of effectiveness or toxicity, the patient can receive Phase 2 therapy. For patients who have prognostically unfavorable factors, such as rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA), very high disease activity, or early joint damage, a biologic agent should be added as current practice. A JAK inhibitor (JAKi) is also an option; however, a bDMARD should be used initially because of the longer experience compared with tsDMARDs. If prognostically unfavorable factors are absent, treatment should be changed to a second csDMARD strategy of leflunomide, sulfasalazine, or methotrexate, alone or in combination, ideally continuing with the glucocorticoid option. These treatment options should be maintained for 6 months. If it is not achieved in patients without prognostically unfavorable factors, a switch to the regimen for patients with unfavorable factors is recommended. If the target is achieved, the regimen can be continued.

Patients who fail Phase 2 for lack of effectiveness or toxicity can proceed to Phase 3. If a bDMARD was used in Phase 2, it should be changed with a different bDMARD, which may include a trial of a different TNFi. When applicable, a second TNFi or a JAKi can be used. The recommendations note that, in the event additional JAKis are available, data regarding efficacy and safety of a second JAKi after inadequate response to an initial JAKi are not available. If the target is not achieved within 6 months, a cycle among bDMARD and tsDMARD is recommended.

Are there any notable comparisons between the EULAR and ACR guidelines?

There are no major differences between the current EULAR and the 2015 ACR guidelines. The ACR guidelines use response to determine treatment recommendations; that is, they do not use prognostic factors for stratifying therapies. CsDMARD monotherapy is strongly recommended over triple therapy, and MTX is the preferred initial csDMARD for DMARD-naive patients with early RA. Using a second TNFi is more advocated in the ACR guidelines for moderate or high disease activity after single TNFi failure, with a non-TNFi biologic as the second option. In addition, the EULAR guideline update is more specific about the use of glucocorticoids, and describes several glucocorticoid treatment strategies.

Please discuss the current EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis.

All rheumatologists rely on baseline plain films of the hands and feet. The EULAR recommendations add that ultrasound and/or MRI should be considered if conventional radiographs do not show damage, and may detect damage at an earlier time.

Imaging, and in particular musculoskeletal ultrasound, is a convenient, effective tool to confirm or eliminate the presence of ongoing inflammation in patients who continue to have symptoms despite what appears to be highly effective treatment. A power Doppler-detected synovitis can help identify patients who are at greater risk of joint destruction in the absence of joint pain or symptoms.

The EULAR imaging recommendations include using conventional radiography, ultrasound, or MRI to improve the certainty of RA diagnosis above using clinical criteria alone when there is diagnostic doubt.
I believe ultrasound is most useful in differential diagnosis of patients with persistent pain or symptoms I cannot understand, but do not believe to have RA. Alternatively, a patient with a stable exam but with continuing and morning symptoms may show several findings on musculoskeletal ultrasound.

In some situations, MRI is very useful in addition to ultrasound, by revealing inflammation and joint damage that may not be apparent by ultrasound.

Prevention of Rheumatoid Arthritis

Please discuss ongoing studies to prevent the development of RA and the role of infectious agents, immunologic factors, and hormonal factors in the etiology of this disease.

The elements of RA that are very well understood are the interaction of the environment with a certain genetic predisposition. This is most striking in patients with ACPA-positive rheumatoid arthritis. There is less evidence on environmental associations with seronegative RA.

The interaction of specific HLA-DR alleles and cigarette smoking is associated with the development of RA and autoimmunity, essentially breaking the tolerance to citrullinated proteins. Chronic bronchial irritation by cigarette smoke leads to bronchitis, with neutrophils moving into the bronchial airway. Airway neutrophils form neutrophil extracellular traps, or NETs, which have been suggested to have an important role in RA. Peptidyl arginine deiminase 4 (PAD4) from the azurophilic granules contributes to NET formation, which is associated with active citrullination of local proteins. Chronic formation of citrullinated proteins in this proinflammatory milieu of the NETs leads to the breaking of tolerance and formation of anti-citrullinated protein antibodies.

These observations led to interest in the possibility that airway or oral pharyngeal organisms can contribute to the formation of citrullinated proteins that lead to breaking tolerance and causing RA in the absence of smoking. Several studies have considered the possible role of Porphyromonas gingivalis in RA. Although the research is in its infancy, some studies have shown an independent relationship between periodontal disease and ACPA-positive RA. However, an association of periodontal disease with RA was not dependent on evidence of prior infection or subgingival colonization with P. gingivalis in some studies, although its influence on ACPA expression requires further study.

Apart from cigarette smoking, there is no evidence to support any other intervention to reduce the risk of RA. Studies of obesity and risk of RA have mixed results. A recent systematic review and meta-analysis that included 11 studies showed a significantly increased risk of RA in obese compared with normal weight subjects. However, prospective studies that can adjust for more confounders are needed. In patients with RA, weight loss has been shown in several studies to improve RA at the level of inflammatory disease.

Are there ongoing key studies to halt the progression of RA?

The preclinical phase of RA is receiving considerable research interest. Circulating autoantibodies can precede clinical disease onset by many years. Studies on the development and identification of these autoantibodies are ongoing. Interest in the mucosal immune response has led to studies of immune cells and autoantibodies in sputum and bronchial alveolar lavage from subjects at risk of developing RA.

The theory that targeting B cells during the preclinical stage may be a preventive approach is being explored in a randomized double-blind trial in persons with serum autoantibodies and elevated CRP levels who are at high risk of developing RA, treated with a single infusion of either rituximab or placebo, and followed for the development of arthritis (PRAIRI study).2 The hypothesis is that treatment will result in a 75% decrease in 4-year RA development. Results from 81 subjects with a median follow-up of 27 months suggest a significant delay in arthritis development was achieved. The StopRA study3 is enrolling similar patients at risk for developing RA, comparing daily hydroxychloroquine with placebo taken daily for 12 months. The development of RA after 3 years is the primary outcome.

Please discuss the evolving role of B-cells in RA.

One of the fascinating questions in RA is that although we use a soluble antibody, ACPA, as the marker of disease severity, progression, and prognosis, there is no clear evidence that it is pathogenic. Several models are proposed, including that autoantibody-complexed B cells are involved, without an effect of the soluble antibody itself. The plausibility of this model is supported by the observation that patients treated successfully with rituximab often do not have a change in circulating ACPA levels. In addition, treatments that decrease autoantibody levels do not necessarily result in a correlated clinical response. Accordingly, depleting the specific B cell subsets targeting ACPA may provide a therapeutic option that has less effect on the overall immune response and risk of infections.

Provide an overview of the currently approved biologic therapies and their effects in halting the progression of the disease.

All of the biologics have been shown to be highly effective for treating RA. They have potent effects on radiographic progression, and improve patient-reported outcomes. However, predictive markers are not yet available to help decide which agent is best for each patient. Accordingly, practitioners must use an empiric stepwise approach, which may include switching from a TNFi that is not effective to a second TNFi, which may prove to provide successful therapy. Head-to-head trials of approved agents are not rigorously pursued; however, once approved, newer effective agents may serve as the active comparator in Phase 3 clinical trials, allowing that level of comparison.

Incorporation of Biomarkers for RA

Although no laboratory test results are pathognomonic for RA, please discuss the importance of incorporating biomarkers such as anti-cyclic citrullinated protein antibodies (ACPAs), rheumatoid factor (RF), sedimentation rate, and C-reactive protein (CRP) into the diagnosis, discussing their specificity and sensitivity, as well as their role in establishing and monitoring the progression or improvement of the condition.

High titer ACPA, RF, and other pro-inflammatory markers are clearly associated with more radiographic progression and worse outcomes. However, most patients with RA are positive for these markers when they first present to health care. Rituximab has been shown to be more effective in seropositive patients. There are less robust data for the new class of JAK inhibitors, the IL-6 inhibitor tocilizumab, and the TNFi. An exploratory analysis of AMPLE study data showed treatment effects for both abatacept and adalimumab were greater in patients who were anti-CCP2 positive at baseline compared with those who were not. Other studies have shown seropositive patients respond less well to TNFi than seronegative patients.

continued on page 18
Use of Biosimilars in Rheumatoid Arthritis

Jonathan Kay, MD

Since the introduction of the first TNF inhibitor in 1998, targeted biological therapies have transformed the treatment of rheumatoid arthritis (RA). However, the high cost of these very effective medications has limited access to them for many patients. To provide these treatments to patients at a lower cost, once patents for the originator biopharmaceutical have expired, biosimilars have been developed. Several biosimilars have been approved by regulatory agencies to treat RA and other inflammatory diseases and are commercially available in many countries.1

A biosimilar is a biopharmaceutical that has been designed to be as close to identical to the reference product (or “bio-originator”) on which it is based.2 Biosimilars are engineered to have the same primary amino acid sequence as the bio-originator and are produced in cell lines chosen for their ability to produce post-translational modifications that are as close as possible to those present on the bio-originator.

Importantly, biosimilars have been subjected to regulatory review by government agencies according to a prespecified pathway for approval of biosimilars, to ensure that the biosimilar is as pure, potent, and safe as its reference product and that there are no meaningful clinical differences between the biosimilar and its reference product. The regulatory pathway for biosimilar approval in the European Union, the United States, and most other countries is abbreviated, compared to that for bio-originators.3,4 Thus, a biosimilar can rely upon the data generated for approval of its reference product, based upon extensive stepwise comparative analytical, in vitro, pharmacokinetic, and pharmacodynamic testing demonstrating that the biosimilar and its reference product are highly similar.

Regulatory agencies review the totality of evidence for a biosimilar, including data from all of the studies comparing the biosimilar to its reference product.5 Notably, a biosimilar can apply for approval in any or all of the indications for which its reference product already has been approved, as long as adequate comparative preclinical data, pharmacokinetic and pharmacodynamic studies, and at least 1 clinical trial in a disease for which the reference biopharmaceutical has been approved demonstrate equivalence of the biosimilar to the reference product. Thus, once a biosimilar has been granted marketing approval, it can be considered to be essentially the same biopharmaceutical as its reference product. Based upon this demonstration of equivalence, regulatory agencies allow biosimilars extrapolation of indications, usually granting the biosimilar approval in indications for which its reference product is approved but in which the biosimilar has not been studied.

On the other hand, copies of biopharmaceuticals that have not undergone regulatory review according to a defined regulatory pathway for approval of biosimilars are not true biosimilars.2 Such copies are “biomimics.” Several of these are marketed in a number of countries, including China, Colombia, India, and Mexico.

Biosimilars of infliximab and etanercept are marketed in many countries to treat patients with RA and other inflammatory diseases. A biosimilar infliximab, CT-P13, was the first biosimilar monoclonal antibody approved by a regulatory agency. After extensive analytical and in vitro studies comparing CT-P13 to reference infliximab, this biosimilar was compared to its reference product in a Phase I randomized controlled pharmacokinetic study (PLANETAS), in which either biosimilar or reference infliximab was administered as monotherapy to 250 patients with ankylosing spondylitis.6 Subsequently, CT-P13 was compared to reference infliximab in a Phase 3 clinical trial (PLANETRA), in which 606 patients with RA received either biosimilar or reference infliximab in combination with methotrexate.7 In PLANETAS, pharmacokinetic equivalence of CT-P13 and reference infliximab was proven. In both clinical trials, CT-P13 was demonstrated to have equivalent efficacy and comparable safety to reference infliximab.

In 2012, CT-P13 was granted approval in South Korea and, in 2013, it was the first biosimilar monoclonal antibody approved in the European Union. Regulatory approval in other countries followed, and it is now marketed as an approved biosimilar in more than 70 countries worldwide.2 In addition to RA and ankylosing spondylitis (AS), CT-P13 has been approved for use in indications for which the bio-originator was approved but in which CT-P13 was not studied: psoriatic arthritis (PsA), Crohn’s disease (CD; adult and juvenile), and ulcerative colitis (UC; adult and juvenile).8 Initially, because of concern about slight differences in antibody-dependent cell-mediated cytotoxicity between CT-P13 and reference infliximab, Health Canada did not approve CT-P13 for use in patients with CD or UC.9 However, in 2016, Health Canada granted CT-P13 approval to treat patients with inflammatory bowel diseases, thereby allowing extrapolation of indications for CT-P13 to all diseases for which reference infliximab is approved.10

Another biosimilar infliximab is SB2, which in a Phase III randomized controlled clinical trial conducted in 584 patients with RA inadequately responsive to methotrexate was shown to have equivalent efficacy and comparable safety to reference infliximab.11 SB2 has been granted regulatory approval and marketed in South Korea and in the European Union for all of the indications for which reference infliximab is approved.12

Likewise, SB4 is a biosimilar etanercept that was shown to have equivalent efficacy and comparable safety to reference etanercept in a Phase III randomized controlled clinical trial conducted in 596
patients with RA inadequately responsive to methotrexate. 15 SB4 has been granted regulatory approval and is marketed in South Korea to treat patients with RA, axial spondyloarthritis (AS), psoriasis (PsO), and psoriatic arthritis (PsA), and in the European Union to treat patients with RA, AS, non-radiographic AS, PsO, and PsA. 14

The US Food & Drug Administration (FDA) has approved the biosimilar infliximab CT-P13 (infliximab-dyyb), 15 the biosimilar etanercept GP2015 (etanercept-szpz), 16 and the biosimilar adalimumab ABP 501 (adalimumab-atto). 17 Because of ongoing patent litigation, none of these 3 biosimilar TNF inhibitors has yet become commercially available in the United States. However, in September 2016, a federal judge ruled in the lawsuit brought by Janssen against Celtrion that Johnson & Johnson’s patent for infliximab is invalid. 18 This has cleared the way for the commercial launch of Inflectra, which will be marketed by Pfizer in the United States.

The availability of biosimilars has raised concern about nonmedical switching, in which patients are transitioned from 1 drug to another for reasons other than loss of efficacy or toxicity of the initial medication. The Biologics Price Competition and Innovation (BPCI) Act of 2009, which established the pathway for biosimilars approval in the United States, defines an interchangeable biosimilar as one that may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product (Table). 19 However, the FDA has not yet issued guidance as to what data will be required for a biosimilar to be granted this designation. Nonetheless, as now occurs with bio-originators, insurance carriers and pharmacy benefit management companies likely will incentivize switching between bio-originators and biosimilars and between 2 biosimilars of the same reference product for purely financial motives. Thus, it will be essential that postmarketing pharmacovigilance studies be conducted to assess immunogenicity and safety of biosimilars with repeated switching in clinical use over an extended time period.

The advantage of using a biosimilar, instead of its reference product, is purely economic. 20 The availability of biosimilars should decrease the cost of treating an individual patient, since it is expected that the biosimilar will cost less than the reference biopharmaceutical.

An individual patient should accept a lower-cost biosimilar so that comparable medications are more widely available to all members of society.

The potential risk to the individual of switching to a lower-cost biosimilar should be outweighed by the potential benefit to society of expanding access to care for all.

However, if the availability of lower-cost biosimilars allows more patients to be treated with a biologic agent, rather than with a relatively inexpensive small molecule drug (such as a traditional disease-modifying antirheumatic drug), the overall cost to the health care system may be greater because more patients would be treated with biopharmaceuticals. This potentially increased overall cost must be offset by a resulting reduction in the morbidity and mortality of RA and other inflammatory diseases.

References

Management of Rheumatic Complications

The irAEs that related to rheumatic diseases may be transient or chronic. Management may require high-dose glucocorticoids, which usually is accompanied by rapid symptom resolution, and biologic therapy is rarely needed.1,22

The FDA approved a risk evaluation and mitigation strategy (REMS) to facilitate understanding the risks associated with the anti-CDLA-4 agent ipilimumab that included an irAE management guide.25 The more extensive clinical data available for this agent contributed to management algorithms for the subsequently approved PD-1 checkpoint agents.15 Appropriate management and follow-up have been recommended based on irAE grade. In general, for musculoskeletal irAEs, recommendations include initiating systemic corticosteroids at a dose of 1 to 2 mg/kg/day (Table on page 7).18 If the irAE is refractory to steroids, immunosuppression with anti-TNFα may provide immediate therapeutic effect.8 Improving our understanding and management of irAEs requires close collaboration between oncologists and specialists who treat conditions characterized by these potential complications.

Summary

Immune checkpoint inhibitors have provided an important addition to the armamentarium for treating several major cancers. These agents target the immune system and not the tumor; accordingly, their efficacy and safety are related to the patient’s immune response capability, and their use can be associated with irAEs, including rheumatic complications.18 Clinical trial data are being supplemented by reports of rheumatic irAEs encountered in clinical practice, which should help raise awareness of these potential complications, and exemplify the need for practitioners to be attentive to their identification and diligent in their management.26 Oncologists should be prepared to refer patients with irAEs to an appropriate specialist for management, as warranted.

References


Focus on Early RA—A 2016 Interview

What is the current role of biomarkers 14-3-3 and MBDA in the management of RA?

The ubiquitous 14-3-3 proteins are usually intracellular; however, the 14-3-3η isoform is expressed extracellularly in joints of patients with RA, and serum and joint fluid expression correlates with the expression of metalloproteinases. Data are emerging on its association with treatment success in RA. Although much additional research is needed, positivity was reported to be associated with a worse initial disease state, and decreased levels after treatment were associated with better clinical outcomes.

The multi-biomarker disease activity (MBDA) score combines serum concentrations of 12 biomarkers using a validated algorithm to produce a 100-point score that quantifies RA disease activity to reflect clinical response to therapy with non-biologic DMARDs. The MBDA score has been shown to be effective for predictive disease activity for Phase 1 patients, methotrexate-naive, methotrexate-inadequate responders, and may have value for TNF-IR. Its effectiveness with the other agents is not clear. Low values have been shown to correlate with good outcomes in microradiographic progression, while high scores are associated with more radiographic progression. A recent study showed that measuring the MBDA score before and during treatment was useful for assessing individual patient risk for radiographic progression during 2 years of follow-up. When response was compared among methotrexate non-responders who received either triple therapy or anti-TNF, those with a high baseline or 3-month MBDA score had a significantly higher rate of radiographic progression at year 2 in the triple therapy group compared with the anti-TNF group. If this data trend continues, the MBDA score will have a valuable application in RA management.

References

1. Specialized, mature dendritic cells express co-stimulatory cell surface molecules (B7) in the presence of infection, binding to which of the following on naïve T cells.
   A. CD7
   B. CD14
   C. CD21
   D. CD28

2. T cells are induced to proliferate and differentiate into effector T cells, by the autocrine action of:
   A. IL-2
   B. IL-3
   C. IL-4
   D. IL-5

3. Which receptor has an affinity for B7 that is approximately 20-fold greater than that of CD28?
   A. CTLA-2
   B. CTLA-3
   C. CTLA-4
   D. CTLA-5

4. Which of the following best describes the mechanism of action for abatacept?
   A. Monoclonal antibody against cell surface CTLA-4
   B. Blocks T cell CD28 from binding with its ligand, inhibiting the co-stimulatory signal of T cell activation
   C. Monoclonal T cell antibody
   D. Enhances binding of CD14 promoting T cell activation

5. Which of the following is a monoclonal antibody against cell surface CTLA-4?
   A. Pembrolizumab
   B. Nivolumab
   C. Ipilimumab
   D. Atezolizumab

6. Which of the following is a monoclonal antibody against PD-L1?
   A. Pembrolizumab
   B. Nivolumab
   C. Ipilimumab
   D. Atezolizumab

7. The first FDA approval of an immunotherapy combination for treating cancer was:
   A. Nivolumab/pembrolizumab
   B. Atezolizumab/ipilimumab
   C. Nivolumab/ipilimumab
   D. Ipilimumab/pembrolizumab

8. Rheumatic complications in patients with cancer treated with checkpoint inhibitors have an incidence estimated at approximately what percentage?
   A. 1%
   B. 5%
   C. 10%
   D. 15%

9. Which of the following PDE4 inhibitors is indicated for treating adults with active psoriatic arthritis and patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy?
   A. Tofacitinib
   B. Filgotinib
   C. Apremilast
   D. Baricitinib

10. You are treating a 62-year-old female with moderate-to-severe active rheumatoid arthritis who has had an inadequate response to methotrexate. Based on current FDA indications, which therapeutic agent would be the most prudent to initiate?
    A. Corticosteroids
    B. Tofacitinib
    C. Ipilimumab
    D. Apremilast
CME Registration Form

Answer Sheet

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Time spent on this activity: Hours ___ Minutes ___ (Reading articles and completing the learning assessment and evaluation.) This information MUST be completed in order for the quiz to be scored.


PRINT OR TYPE

Last Name First Name Degree

Mailing Address

City State Zip Code

Date of Birth (used for tracking credits ONLY)

Phone Number \( \text{FAX Number} \)

E-mail Address

Activity Evaluation

Your evaluation of this activity is extremely important as it allows for us to plan for future educational programs. Please take a moment to answer the following questions.

How many years have you been treating patients with rheumatoid arthritis (RA)?

☐ >10 ☐ 10 to 20 ☐ 21 to 30 ☐ More than 30 ☐ N/A

Approximately how many patients with RA do you see per month?

☐ 1 to 9 ☐ 10 to 30 ☐ 31 to 50 ☐ More than 50 ☐ N/A

Please rate the overall educational quality of this activity (from 5=Excellent; 1=Poor)

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

1. Overall, the activity supported achievement of the identified learning objectives.
2. This activity better prepared me to care for my patients.
3. The content covered was useful and relevant to my practice.
4. Future activities concerning this subject matter are necessary.
5. The activity addressed and provided strategies for overcoming barriers to optimal patient care.
6. The activity reinforced my current practice patterns.
7. The activity was presented objectively and was free of commercial bias.

*If you indicated that the activity WAS NOT free of commercial bias, please provide additional comments here:

__________________________________________________________________________

__________________________________________________________________________

Do you believe this program:

Increased your knowledge about the subject matter? ☐ Yes ☐ No ☐ N/A

Increased your competence in managing these patients? ☐ Yes ☐ No ☐ N/A

Will improve your performance in caring for your patients? ☐ Yes ☐ No ☐ N/A

Will improve patient outcomes in your practice? ☐ Yes ☐ No ☐ N/A

Provided you with resources to use in your practice and/or with your patients? ☐ Yes ☐ No ☐ N/A

What did you like about this program?
It allowed me to interact with my peers and faculty. ☐ Yes ☐ No ☐ N/A

It provided information in ways that I can review again later. ☐ Yes ☐ No ☐ N/A

It gave me the opportunity to apply information to realistic scenarios I confront in practice. ☐ Yes ☐ No ☐ N/A

It facilitated the sharing of experiences and best practices. ☐ Yes ☐ No ☐ N/A

Planned Changes to Practice

Please respond to the statements below using the following scale:

Y=Yes, N=No, 3=I Already Do This in My Practice, 4=N/A

Y ☐ N ☐ 3 ☐ 4 ☐

I plan to make the following changes to my practice:

Assess patient’s progression of RA from asymptomatic autoimmunity to pre-RA and RA. ☐ Y ☐ N ☐ 3 ☐ 4 ☐

Consider immune-based management strategies for patients with rheumatic diseases. ☐ Y ☐ N ☐ 3 ☐ 4 ☐

Implement strategies to mitigate risk from biologic and immune-based therapies when treating patients with RA. ☐ Y ☐ N ☐ 3 ☐ 4 ☐

Remain aware of current and emerging treatments for the management of rheumatic diseases. ☐ Y ☐ N ☐ 3 ☐ 4 ☐

Consider the use of biosimilars for patients with RA. ☐ Y ☐ N ☐ 3 ☐ 4 ☐

Other (Please provide below.)

How confident are you in your ability to manage your patients with RA (select ONE)?

☐ Extremley Confident ☐ Very Confident

☐ Somewhat Confident ☐ Not at All Confident

Please rate your level of confidence concerning your understanding of the specific mechanisms of action for current biologic therapies. (select ONE)

☐ Extremley Confident ☐ Very Confident

☐ Somewhat Confident ☐ Not at All Confident

I vaccinate my patients with rheumatoid arthritis who are receiving methotrexate for influenza yearly.

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

Which region of the country do you live in?

☐ Northeast ☐ Midwest ☐ Southeast ☐ Southwest ☐ West

What is your practice setting?

☐ Academic ☐ Hospital ☐ Health care organization

☐ Multi-specialty group practice ☐ Single-specialty group practice

☐ Solo practice ☐ Outpatient clinic ☐ Other: _________________

What educational topics would be of value to you for future CME activities?

Please be specific.

__________________________________________________________________________

Help us make our CME activities better by providing any additional comments here:

__________________________________________________________________________

__________________________________________________________________________

Approximately what percentage of the activity’s content was NEW to you?

☐ 0% ☐ 25% ☐ 50% ☐ 75% ☐ 100%

Would you recommend this activity to your peers? ☐ Yes ☐ No

__________________________________________________________________________

__________________________________________________________________________

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